UNIVERSIDADE DE LISBOA

Faculdade de Medicina

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Carla Cristina Paulo Gabriel Bentes

Orientadores: Prof. Doutor José Manuel Morão Cabral Ferro

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Tese especialmente elaborada para obtenção do grau de Doutor em Medicina, ramo de Neurologia

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Aos meus Pais

À Catarina, ao Francisco, ao Afonso e ao Duarte

Ao Filipe

PREAMBLE

"It is important to learn; but it is much more important to learn how to learn,
and to desire to go on learning all through life"
Pedro Arrupe

O meu gosto pela Neurologia começou em 1988 na Faculdade de Medicina da Universidade de Lisboa, à qual me proponho agora para obtenção do grau de Doutor. O início aconteceu durante a cadeira de Anatomia II com o Professor Doutor António Gonçalves Ferreira, cresceu e amadureceu significativamente na cadeira de Neurologia pela mão do meu assistente, o Dr. Francisco Pinto e fortificou-se no 6.º ano na cadeira de Neurocirurgia por influência marcante do Professor Doutor João Lobo Antunes.

Desde então, não mais parei de me entusiasmar pelas infindáveis potencialidades e mistérios do Sistema Nervoso. Esta paixão alimenta-se dia-a-dia com o apoio de Neurologistas extraordinários com os quais tenho tido o privilégio de percorrer este caminho. Logo nos primeiros anos do internato, no Serviço de Neurologia do Hospital de Santa Maria, a Professora Doutora Maria de Lurdes Salles Luís e o Professor Doutor Mamede de Carvalho deram-me a conhecer a Neurofisiologia e mudaram por completo a minha forma de estar e pensar em Neurologia. O entusiasmo foi tão forte e evidente que a minha diferenciação nesta área foi perfeitamente natural, como se nunca pudesse ter escolhido outro campo de diferenciação na Neurologia. Houve ainda uma influência fundamental do Grupo de Estudos da Epilepsia do Serviço e do Grupo da Cirurgia da Epilepsia, na altura ainda no seu inicio (com o Professor Doutor António Gonçalves Ferreira, Professor Doutor Carlos Garcia, Dr. Francisco Pinto e Professora Doutora Maria Sande Lemos). Alguém muito especial no meu percurso foi, sem dúvida, a Professora Doutora Teresa Paiva, responsável pelo Laboratório de EEG/Sono onde fiz o meu estágio de Neurofisiologia, primeiro obrigatório e depois opcional, e onde continuei a trabalhar desde então. Foi desta forma que durante o internato conheci o mundo aliciante, os factos e os enigmas de duas áreas neurológicas em franco desenvolvimento, a Epilepsia e o Sono, aliados inseparáveis da Neurofisiologia Clinica, e que dei o primeiro passo de uma viagem que me trouxe até aqui. Realço ainda o Professor Doutor Colin Binnie e a Dr. Nandini Mullati com os quais tive oportunidade de trabalhar no King´s College Hospital em Londres, meus mentores no gosto e diferenciação em Neurofisiologia Clínica e estudos neurofisiológicos no doente com epilepsia.

O meu percurso académico esteve lado a lado com a minha formação e vida hospitalar e muitas vezes foi exatamente o mesmo. Durante o curso de Medicina, dei tímidos passos na investigação laboratorial com a Professora Doutora Leonor Parreira e Professora Doutora Carmo Fonseca no Laboratório de Biologia Celular, nessa altura da responsabilidade do Professor Doutor David Ferreira. Posteriormente, tive o privilégio de me formar e depois adquirir um vínculo de trabalho num Serviço onde a investigação, o ensino e clínica viviam

e vivem em harmonia, complementando-se numa relação de simbiose autossustentável e gratificante. Foi então essencial, uma vez mais, a influência do Professor Doutor Mamede de Carvalho com quem dei os primeiros passos na comunicação e publicação em Ciência. Com uma mente brilhante e uma motivação inesgotável, o Professor Doutor Mamede de Carvalho será sempre uma referência na minha vida profissional. Agradeço-lhe todos os minutos em que me ensinou Neurofisiologia e Ciência. Sem eles, a minha vida profissional teria seguido, certamente, um rumo diferente. Mais tarde, o Professor Doutor José Pimentel e a Professora Doutora Teresa Paiva incentivaram o meu interesse pela investigação em epilepsia e medicina do sono, respectivamente. Por outro lado, o meu gosto em ensinar (provavelmente genético) e pela formação médica sempre esteve presente. Desde cedo a minha colaboração voluntária nas aulas práticas de neurologia foi um estímulo para o meu próprio crescimento e aprendizagem. Sempre, a Professora Doutora Teresa Paiva e o Professor Doutor José Pimentel incentivaram este meu gosto e proporcionaram-me diferentes experiências curriculares na formação pré e pós-graduada, médica e não médica, dentro e fora da Faculdade de Medicina da Universidade de Lisboa, que enriqueceram a minha própria formação.

Desde o final do internato que tinha a intensão de prosseguir para o doutoramento. Outros projetos e imponderáveis foram protelando a decisão de o iniciar. Achei que precisava de me tornar formalmente neurofisiologista pelo que fiz o Ciclo de Estudos Especiais em Neurofisiologia Clínica, ganhando progressivamente prática na interpretação dos exames neurofisiológicos. Estive 4 anos num hospital distrital, numa “vaga de carenciados”, onde aprendi outra realidade sobre a medicina e em particular sobre a Neurologia em Portugal. No Ribatejo, fiz ainda alguns amigos. Constituí a minha própria família, numerosa por opção. Assumi precocemente a responsabilidade de um Laboratório de EEG/Sono e de uma consulta externa num Departamento de Neurociências de um Hospital Universitário e, por este motivo, decidi fazer uma pós-graduação em liderança e gestão de unidades de saúde. Não foi tempo perdido, foi tempo ganho a adquirir outras capacidades, competências, atitudes e a construir um curriculum, principalmente “escondido”, que muito me tem ajudado a fazer a minha viagem profissional, clinica e académica, e a construir a pessoa que sou hoje.

A decisão de juntar o EEG, a Epilepsia e as Doenças Vasculares Cerebrais numa tese de doutoramento tem naturalmente a influência e a liderança perspicaz do Professor Doutor José Manuel Ferro, Diretor do Departamento de Neurociências onde trabalho. O tema não

era algo totalmente novo no meu percurso clinico e académico, tendo já trabalho publicado desde 2001 não só sobre crises e epilepsia pós-AVC [1,2], sob a orientação do Professor Doutor José Manuel Ferro, mas também sobre recomendações na utilização do EEG em epilepsia [3], com a orientação do Professor Doutor António Martins da Silva. Agora, a vertente neurofisiológica, já mais amadurecida, foi adicionada ao tema. Tive como principal objetivo sair um pouco da minha zona de conforto para conseguir aprender mais sobre investigação clínica e método científico. Queria aprender mais para conseguir um dia ensinar melhor. Começar do início, de uma hipótese, projetar, escrever e desenvolver um projeto original, implementá-lo na prática clínica multi e interdisciplicarmente, utilizar diferentes técnicas e métodos de análise em investigação clinica e neurofisiológica, recolher dados e analisá-los corretamente, escrever, escrever e reescrever, tantas vezes quanto o meu sentido crítico exigisse, aprender a lidar com a revisão por pares ao ponto de se tornar um desafio viciante e gratificante e, no final, conseguir resumir vários anos de trabalho num texto de 1200 palavras ou em 20 minutos de apresentação. Estas foram as minhas prioridades na escolha do tema da tese e do meu orientador. Estava consciente de que para adquirir um novo Saber era preciso "desaprender" primeiro, relativizar algumas coisas que sabia ou pensava que sabia, começar de novo com alguém que me questionasse por tudo, que fosse mais exigente do que eu própria e que me permitisse abandonar alguns hábitos, mas principalmente criar outros. Sendo uma referência Nacional e Internacional, Clínica e Académica, na área da Neurologia e Doenças Vasculares Cerebrais, com um gosto secreto pela Epilepsia (gosto de acreditar que sim...), quem melhor do que o Professor Doutor José Manuel Ferro para me fazer sair da minha zona de conforto? Agradeço-lhe ter-me acolhido nesta área e a confiança que em mim depositou ao aceitar o desafio de ser meu orientador. Peço-lhe desculpa por todos os e-mails ao fim-de-semana e por todos os textos e pedidos de assinaturas para submissão de artigos, que lhe enviei quando estava de férias. A orientação conjunta da Professora Doutora Teresa Paiva surgiu naturalmente. Não teria sentido de outra forma. Muito do que aprendi e continuo a aprender sobre Neurofisiologia, Sono e sobre a Vida em geral devo à Professora Doutora Teresa Paiva. Tenho imenso orgulho em fazer parte da Escola que formou, e continua a formar, e de merecer a sua amizade.

A escolha do tema da tese teve ainda dois outros motivos subjacentes, mutuamente relacionados. Sendo uma tese de doutoramento em Neurologia, fazia-me sentido que englobasse e integrasse diferentes áreas do conhecimento neurológico de uma forma concertada. Por outro lado, tem sido meu objetivo abrir as portas do Laboratório de EEG/Sono onde trabalho a outras áreas da Neurologia, convicta que a Neurofisiologia e a

Medicina do Sono são áreas transversais e essenciais às Neurociências (e não ilhas isoladas), e que todas ganham com o contributo multi e interdisciplinar. A colaboração com grupo de Doenças Vasculares Cerebrais do Serviço de Neurologia, ao qual agradeço a oportunidade que me foi dada, foi um exemplo bem sucedido disso mesmo. Este projeto de doutoramento foi pensado e planeado para que pudesse ocorrer no dia-a-dia de um Serviço de Neurologia, tanto na sua vertente ambulatória como de internamento, com os recursos humanos, técnicos, logísticos e de espaço previamente existentes (na verdade foi feito em plena *troika*...). A organização do Laboratório com esse objetivo foi um exercício muito interessante de gestão e liderança e permitiu que o laboratório se tornasse mais eficiente, antecipando o crescente número de exames eletroencefalográficos que foram requisitados que nos anos seguintes, principalmente a doentes internados.

Será certamente não o fim, mas um novo princípio. Quero levar o que aprendi a outras áreas a que me dedico na Neurologia e Neurofisiologia, principalmente no âmbito da Epilepsia e da Medicina do Sono. Quero poder ensinar o que aprendi e, sobretudo, quero continuar a aprender.

CB

Setembro de 2017

TITLE/ABSTRACT/KEY-WORDS

“If you can't explain it simply, you don't understand it well enough”

Albert Einstein

The EEG in Acute Ischaemic Cerebrovascular Disease

The electroencephalogram (EEG) is a neurophysiological technique with high temporal resolution and sensibility in the evaluation of brain function in real time. Besides this, EEG is the *gold standard* for the identification of epileptogenesis and ictogenesis biomarkers.

Epileptic seizures and Cerebrovascular disease are two of the most frequent neurological disorders imposing important mutual challenges. Furthermore, in recent years, stroke care has evolved remarkably and, facing a new paradigm of acute standard of care (centred on multidisciplinary Stroke Units), epileptic seizures (as stroke complications) deserve to be rethought. The EEG is an essential neurophysiological exam in the evaluation of patients with epileptic seizures, status epilepticus and/or epilepsy, both for diagnosis and classification, as well as for the establishment of a correct treatment or outcome prediction. Furthermore, EEG has been previously used in cerebrovascular disease with different purposes. However, its clinical usefulness in the differential diagnosis of transient neurological symptoms, specifically in the differentiation between a transient ischaemic attack and some epileptic seizures, and also in the diagnosis or prediction of post-stroke seizures or in post-stroke prognosis prediction, remains uncertain.

In this work, we aim to use the clinical model of acute ischaemic cerebrovascular disease to study the value of EEG in the differential diagnosis of transient neurological symptoms, in the diagnosis and prediction of post-stroke seizures and epilepsy, as well as to analyse if electroencephalographic abnormalities and/or epileptic seizures are independent predictors of an anterior circulation ischaemic stroke outcome. Furthermore, since the *gold standard* of acute stroke care (namely intravenous alteplase treatment) is associated with a reduction of mortality and incapacity of treated patients with possible consequences in post-stroke seizure frequency, but a pro-convulsive and an epileptogenic effect of alteplase has also been described, we aim to test the hypothesis that ischaemic stroke patients treated with intravenous alteplase have a different frequency of epileptic (clinic and/or electroencephalographic) manifestations compared to non-treated patients.

Different research methodologies were used in this thesis. A systematic review and meta-analysis of observational studies was performed to evaluate both the frequency of post-stroke (ictal and interictal) epileptiform activity in the EEG, and the quality of studies about this

subject. Furthermore, different types of observational studies (including clinical case report, case series and cohort studies) were completed to answer relevant clinical questions.
We performed a prospective longitudinal study of possible transient ischaemic attacks (TIA) patients evaluated at a tertiary centre during 36 months, with 1-3 months follow-up and also of acute anterior circulation ischaemic stroke patients, consecutively admitted to a Stroke Unit over 24 months and followed-up for one year. In both studies, patients underwent standardized clinical, diagnostic and neurophysiological assessment.
A short duration (≤60 minutes) video-EEG protocol with an extended montage including 64 EEG, two electrooculogram, one electrocardiogram and at least one electromyogram channel was established. Different electroencephalographic investigation technics including visual, back-average and quantitative analysis were used in the clinical workup of patients with possible and definite, transient and established, cerebrovascular disease as tools for the differential diagnosis and for brain functional assessment, concerning not only epileptic manifestations detection and prediction but also to search for predictors of ischaemic stroke functional outcome and vital prognosis.

Although epileptic seizures were the most frequent defined final diagnosis (n=13; 16.3%) in our series of 80 patients with difficult-to-diagnose transient neurological symptoms, visual inspection of EEG supported this diagnosis only in 7.5% (n=6) of patients with possible TIA. Moreover, the majority (n=6; 53.8%) of patients with the final diagnosis of epileptic seizures did not have interictal epileptiform activity in an early EEG. Furthermore, early focal slow wave activity, the most frequent EEG abnormality in this patient's series, did not distinguished between TIA and seizure patients.
Our systematic review and random-effects meta-analysis showed that the pooled frequency of post-stroke ictal and interictal epileptiform activity was 7% (95%CI: 3%-12%) and 8% (95%CI: 4%-13%) respectively. Only 2 out of 17 included studies (11.7%) attained the maximum quality score. Moreover, no study exclusively enrolled ischaemic stroke patients, highlighting the need for higher quality studies in the evaluation of epileptiform activity frequency in this type of cerebrovascular disease. Furthermore, due to detection bias, it was not possible to correlate clinical and electrographic seizures.
In our prospective cohort of 151 anterior circulation acute stroke patients, we identified different post-stroke, clinical and electroencephalographic, epileptic manifestations including 22.7% (5/22) of acute symptomatic seizures that were exclusively electrographic and therefore could not otherwise be recognised. Furthermore, only EEG back-average

analysis allowed the diagnosis of cortical myoclonus during intravenous alteplase perfusion in one clinical vignette included in this work and the recognition of *epilepsia partialis continua* as a chronic complication of this stroke type in 1.7% of patients. This original work also showed that studied clinical and EEG epileptic manifestations were not significantly different between intravenous alteplase treated and non-treated patients.

This thesis work established which abnormalities of an early EEG after acute stroke (background activity asymmetry and the presence of interictal epileptiform activity) are independent predictors of epilepsy in the year after (even when adjusted for clinical and imaging stroke severity). Besides this, early (within the first 72h) post-stroke EEG features, extracted from visual (background activity diffuse slowing and asymmetry) and quantitative (such as delta-theta to alpha-beta ratio and alfa relative power) analysis were recognized as independent predictors of death or functional dependency, at hospital discharge and at 12 months after stroke. Furthermore, outcome models that incorporate delta-theta to alpha-beta ratio or alpha relative power were better than models based exclusively on clinical and imaging-related ischaemic stroke severity at hospital admission. Additionally, post-stroke acute symptomatic seizures and epilepsy were independently associated to death and to an unfavourable outcome 1 year after an acute anterior circulation ischaemic stroke, respectively.

Globally, these research projects have shown the value of EEG in the current paradigm of stroke patient's care. Furthermore, they expand the knowledge both about the EEG role as a complementary neurophysiological tool in general Neurology and about different aspects of the diagnosis and outcome of two of the most prevalent neurological disorders, Cerebrovascular Diseases and Epilepsy, in particular.

Beyond the value of specific results, with this work several other research questions about EEG and seizures in ischaemic cerebrovascular disease emerge. Therefore, new possibilities of future research, ideally multicentric, clinical or translational arise.

Key-words: EEG, cerebrovascular disease, transient ischaemic attacks, ischaemic stroke, alteplase, intravenous thrombolysis, acute symptomatic seizures, unprovoked seizures, epilepsy, diagnosis, prediction, outcome.

O EEG na Doença Vascular Cerebral Isquémica Aguda

O eletroencefalograma (EEG) é uma técnica neurofisiológica com uma elevada resolução temporal e sensibilidade na avaliação da função cerebral em tempo real. Para além disso, o EEG é o *gold standard* para a identificação de biomarcadores da epileptogénese e ictogénese.

As crises epilépticas e a doença vascular cerebral são duas das doenças neurológicas mais frequentes e que impõem mutuamente desafios importantes. Além disso, nos últimos anos, os cuidados ao doente com AVC evoluíram de uma forma notável e num novo paradigma de cuidados agudos (centrados em equipas multidisciplinares), as crises epilépticas (como complicações pós-AVC) merecem ser re-estudadas. O EEG é um exame neurofisiológico essencial na avaliação de doentes com crises epilépticas, estado de mal epilético e/ou epilepsia, tanto para o diagnóstico e classificação, como para o estabelecimento de um tratamento adequado e predição prognóstica. Para além disso, o EEG foi usado previamente na doença vascular cerebral com diferentes objectivos. Contudo, é ainda incerta a sua utilidade clínica no diagnóstico diferencial dos sintomas neurológicos transitórios, nomeadamente na diferenciação entre um acidente isquémico transitório e alguns tipos de crises epilépticas, e também no diagnóstico ou predição de crises epilépticas após um acidente vascular cerebral (AVC) ou na predição do prognóstico pós-AVC.

Neste trabalho, tivemos como objectivo usar o modelo clínico da doença vascular cerebral para estudar o valor do EEG no diagnóstico diferencial dos sintomas neurológicos transitórios, no diagnóstico e predição das crises pós-AVC, assim como para analisar se as alterações eletroencefalográficas e/ou as crises epilépticas são preditoras independentes do prognóstico num doente com um acidente vascular cerebral isquémico da circulação anterior. Ademais, porque o tratamento atual padrão dos doentes com acidente vascular cerebral isquémico agudo (alteplase endovenosa) está associado a redução da mortalidade e da incapacidade, com possíveis consequências na frequência de crises pós-AVC, mas um efeito pró-convulsivo e epileptogénico da alteplase também foi descrito, quisemos estudar a hipótese dos doentes tratados com alteplase endovenosa terem uma frequência diferente de manifestações epilépticas (clínicas e/ou eletroencefalográficas) comparativamente com os doentes não tratados.

Diferentes metodologias de investigação foram usadas neste trabalho. Foi efetuada uma revisão sistemática e meta-análise de estudos observacionais para avaliar a frequência de atividade epileptiforme (crítica e intercrítica) e a qualidade dos estudos existentes sobre este assunto. Adicionalmente, foram completados diferentes estudos observacionais (incluindo descrição de caso clínico, série de casos e estudos de coorte) respondendo a perguntas clínicas relevantes.

Efetuámos um estudo longitudinal prospectivo de doentes com acidentes isquémicos transitórios possíveis, avaliados num centro terciário durante 36 meses e com 1-3 meses de seguimento. Estudámos ainda doentes com um AVC isquémico agudo da circulação anterior, admitidos consecutivamente numa Unidade de AVC durante 24 meses e seguidos durante 1 ano. Em ambos os estudos os doentes foram submetidos a uma avaliação clínica, diagnóstica e neurofisiológica estandardizada.

Foi estabelecido um protocolo de vídeo-EEG de curta duração (≤60 minutos) com uma montagem que incluía pelo menos 64 canais de EEG, dois de eletrooculograma, um de eletrocardiograma e pelo menos um de eletromiograma. Diferentes técnicas eletroencefalográficas foram usadas na avaliação de doentes com doença vascular cerebral possível ou definitiva, transitória ou estabelecida. Estas ferramentas foram utilizadas para o diagnóstico diferencial e para a avaliação da função cerebral, não só no que diz respeito à detecção e previsão de manifestações epilépticas, mas também à identificação de preditores do prognóstico funcional e vital de doentes com um acidente vascular cerebral isquémico.

Embora as crises epilépticas tenham sido o diagnóstico final definido mais frequente (n=13/16.3%) na nossa série de 80 doentes com sintomas neurológicos transitórios de difícil diagnóstico, a análise visual do EEG suportou este diagnóstico somente em 7.5% (n=6) dos doentes com AIT possível. Aliás, a maioria dos doentes (n=6; 53,8%) com o diagnóstico final de crises epilépticas não tinha atividade epileptiforme no EEG precoce. Por outro lado, a atividade lenta focal precoce, alteração mais frequente no EEG nesta série de doentes, não permitiu o diagnóstico diferencial entre um AIT e uma crise epiléptica.

A revisão sistemática e a meta-análise de efeitos aleatórios efetuadas mostrou uma frequência estimada de atividade epileptiforme crítica e intercrítica de 7% (95%CI: 3%-12%) e 8% (95%CI: 4%-13%), respectivamente. Somente 2 dos 17 estudos incluídos (11,7%) obtiveram uma pontuação máxima na escala de avaliação de qualidade utilizada. Para além disso, nenhum estudo envolveu doentes exclusivamente com AVC isquémico, mostrando a necessidade de trabalhos de melhor qualidade na avaliação da frequência da

atividade epileptiforme neste tipo de doença vascular cerebral. Além disso, devido a um viés de detecção, não foi possível correlacionar as crises clínicas e eletrográficas.

No estudo prospectivo de 151 doentes com AVC isquémicos da circulação anterior, identificámos diferentes manifestações epilépticas pós-AVC, clínicas e eletroencefalográficas, incluindo 22.7% (5/22) de crises sintomáticas agudas que foram exclusivamente eletrográficas e que, portanto, não poderiam ter sido reconhecidas de outra maneira. Da mesma forma, somente a análise de "back-average" permitiu o diagnóstico de mioclonias corticais durante a perfusão endovenosa de alteplase numa vinheta clínica incluída neste trabalho e o reconhecimento de *epilepsia partialis continua* como uma complicação crónica deste tipo de AVC em 1.7% dos doentes. Este trabalho original também mostrou que as manifestações epilépticas estudadas, clínicas e eletroencefalográficas, não foram significativamente diferentes entre doentes tratados e não tratados com alteplase endovenosa, após ajustamento para a idade e gravidade clínica e imagiológica do enfarte.

Esta tese identificou ainda alterações eletroencefalográficas precoces após um acidente vascular cerebral agudo do território anterior (assimetria da eletrogénese de base e atividade epileptiforme intercrítica no EEG) como preditores independentes de epilepsia pós-AVC no ano seguinte (mesmo após ajuste para a gravidade clínica e imagiológica do enfarte). Além disso, características eletroencefalográficas precoces (das primeiras 72h) pós-AVC, extraídas não só da análise visual (lentificação e assimetria da eletrogénese de base) mas também quantitativa do EEG (como o rácio delta-teta / alfa-beta e a potência relativa do alfa) foram reconhecidas como preditores independentes de morte ou dependência funcional, não só na alta como 12 meses depois de um AVC isquémico da circulação anterior. Para além disso, os modelos de prognóstico que incorporaram o rácio delta-theta / alfa-beta ou a potência realtiva do alfa tiveram uma melhor capacidade discriminativa do que o modelo baseado exclusivamente na gravidade clínica e imagiológica do enfarte aquando da admissão hospitalar do doente com um AVC agudo do território anterior. Adicionalmente, as crises sintomáticas agudas e a epilepsia pós-AVC associaram-se a morte e a um prognóstico desfavorável, respetivamente, no ano seguinte a um AVC agudo da circulação anterior.

Na sua globalidade, os projetos de investigação incluídos nesta tese mostraram o valor do EEG no paradigma atual dos cuidados médicos ao doente com AVC isquémico. Ademais, ampliam o conhecimento sobre o valor do EEG como uma técnica neurofisiológica complementar em Neurologia e sobre o diagnóstico e prognóstico de duas das mais prevalentes doenças neurológicas, as Doenças Vasculares Cerebrais e a Epilepsia.

Para além do valor dos resultados específicos, surgem com este trabalho várias outras perguntas de investigação sobre o EEG e as crises epilépticas pós AVC. Emergem assim novas possibilidades de investigação futura, idealmente multicêntrica, clínica e translacional.

Palavras-Chave: EEG, doença vascular cerebral, acidente isquémico transitório, AVC isquémico, alteplase, trombólise endovenosa, crises sintomáticas agudas, crises não provocadas, epilepsia, diagnóstico, predição, prognóstico.

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“If you want to go fast, go alone. If you want to go far, go together”

African Proverb

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SCIENTIFIC BOARD and ETHICS COMMITTEE APPROVALS

"Science is a way of thinking much more than it is a body of knowledge"

Carl Sagan

"Ethics is nothing else than reverence for life"

Albert Schweitzer

The Scientific Board of Faculty of Medicine - University of Lisbon on September 20th 2011, approved this CAML PhD project

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“Money is not the only answer, but it makes a difference”

Barack Obama

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INSTITUTIONS WHERE PROJECTS WERE PERFORMED

"Be sure you put your feet in the right place, then stand firm"

Abraham Lincoln

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1.1. EEG/Sleep Laboratory (all projects)

1.2. TIA Clinic (project 1)

1.3. Stroke Unit (project 1, 3, 4, 5, 6, 7, 8 and 9)

2. Faculty of Medicine, University of Lisbon. Lisboa, Portugal

2.1. Neurology University Clinic (all projects)

2.2. Centre for Evidence-Based Medicine (project 2)

CO-AUTHORS, AFILLIATIONS and CONTRIBUTIONS

“A nossa vida que parece uma linha recta, não o é.
Construímos a nossa vida só uns 5%,
o resto é feito pelos outros, porque vivemos com os outros”
José Saramago

The following co-authors contributed to the projects and publications contained in this PhD thesis:

Professor Doutor José M. Ferro, affiliated to Department of Neurosciences and Mental Health (Neurology) at Hospital de Santa Maria-CHLN and Faculty of Medicine-University of Lisbon in Lisboa, Portugal, contributed fully in all projects included in this thesis, in particular in study conception and design, intellectual input to analysis and interpretations of data and critical revision of all manuscripts. Professor Doutor José Ferro made a critical revision of this thesis.

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in study conception and design, intellectual input to interpretation of data and critical revision of manuscripts. Dr. Teresa Pinho e Melo also contributed to projects 1 included in this thesis, in particular in data acquisition, intellectual input to interpretations of data and critical revision of manuscripts.

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Professora Doutora Ana Catarina Fonseca and Dr. Ruth Geraldes, affiliated to Department of Neurosciences and Mental Health (Neurology) at Hospital de Santa Maria-CHLN and Faculty of Medicine-University of Lisbon in Lisboa, Portugal, contributed in projects 1, 3, 4 and 6 to 9 included in this thesis, in particular in data acquisition, interpretation of data and critical revision of all manuscripts. Dr. Ruth Geraldes is currently affiliated to Nuffield Department of Clinical Neurosciences at John Radcliffe Hospital in Oxford, United Kingdom and Anatomy Institute, Faculty of Medicine-University of Lisbon, Portugal.

Dr. Ana Catarina Franco, affiliated to Department of Neurosciences and Mental Health (Neurology) at Hospital de Santa Maria-CHLN in Lisboa, Portugal, contributed in projects 2 to 9 included in this thesis, in particular in data collection and analysis, interpretation of data and critical revision of all manuscripts.

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Dr. Hipólito Nzwalo, affiliated to the department of Biomedical Sciences and Medicine, University of Faro in Faro, Portugal, contributed in project 2 included in this thesis, in particular in data collection and analysis and interpretations of data.

LIST OF PUBLICATIONS

"Not everything that can be counted counts,
and not everything that counts can be counted"
Albert Einstein

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1. *Bentes, C. et al. Usefulness of EEG for the differential diagnosis of possible transient ischaemic attack. Clin. Neurophysiol. Pract. 3,11-19 (2018).

2. Rodrigues, F. B. et al. Post-stroke epilepsy frequency/incidence – a protocol of a systematic review and meta-analysis of observational studies. PROSPERO 2015:CRD42015029362. (2015).

3. Bentes, C. et al. Frequency of post-stroke electroencephalographic epileptiform activity – a systematic review and meta-analysis of observational studies. Eur. Stroke J. 2, 361–368 (2017).

4. Bentes, C. et al. Post-stroke seizures are clinically underestimated. J. Neurol. 264, 1978–1985 (2017).

5. Bentes, C. et al. Epilepsia partialis continua after an anterior circulation ischaemic stroke. Eur. J. Neurol. 24, 929–934 (2017).

6. Bentes, C. et al. Cortical myoclonus during IV thrombolysis for ischaemic stroke. Epilepsy Behav. Case Reports 2, 186–188 (2014).

7. Bentes, C. et al. Epileptic manifestations in stroke patients treated with intravenous alteplase. Eur. J. Neurol. 24, 755–761 (2017).*

8. Bentes, C. et al. Early EEG predicts poststroke epilepsia. Epilepsia Open 3 (2), 441-452 (2018).

9. Bentes, C. et al. Seizures, electroencephalographic abnormalities, and outcome of ischaemic stroke patients. Epilepsia Open 2, 441–452 (2017).**

10. Bentes , C. et al. Quantitative EEG and functional outcome following acute ischaemic stroke. Clinical Neurophysiology 129, 1680-1687 (2018).

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**This article won the Epilepsy Open Prize 2018

INITIALS, ACRONYMS and ABBREVIATIONS

"KISS principle"
Keely Johnson

A

AAS – Acute Symptomatic Seizure(s)

ACA – Anterior Cerebral Artery

ACNS– American Clinical Neurophysiology Society

ADCI – Acute Delta Change Index

AED – Antiepileptic Drug(s)

AP – Absolute Power

ARP – Ana Rita Peralta

ASCI – Acute Symmetry Change Index

ASPECTS – Alberta Stroke Program Early CT Score

AVC – Acidente Vascular Cerebral

B

BA – Background Activity

BAA – Back-Average Analysis or jerk-lock back-average analysis (JLBA)

BSI – Brain Symmetry Index

C

CAML – Centro Académico de Medicina de Lisboa

CB – Carla Bentes

CC – Carlos Casimiro

cEEG – continuous EEG

CHLN – Centro Hospitalar Lisboa Norte

CI – Confidence Interval

CM – Carlos Morgado

CNS – Central Nervous System

CT – Computer Tomography

D

DAR – Delta to Alpha Ratio

DS – Diana Sousa

DTABR – Delta-Theta to Alpha-Beta Ratio

DWI – Diffusion-Weighted brain magnetic resonance Imaging

E

EA – Epileptiform Activity

ED – Emergency Department

EEG – Electroencephalogram or Electroencephalography

EPC – Epilepsia Partialis Continua

ESO – European Stroke Organization

F

FBR – Filipe Brogueira Rodrigues

FFT – Fast Fourier Transform

FIRDA – Frontal Intermittent Delta Rhythmic Activity

FSWA – Focal Slow Wave Activity

G

GSD – Gonçalo Silva Duarte

H

HFF – High Frequency Filter

HN – Hipólito Nzwalo

HSM – Hospital de Santa Maria

HSM-CHLN – Hospital de Santa Maria - Centro Hospitalar Lisboa Norte

Hz – Hertz

I

ICU – Intensive Care Unit

i.e. – *id est* ("that is.")

IEA – Interictal Epileptiform Activity

ILAE – International League Against Epilepsy

IQR – InterQuartile Range

J

JLBA –Jerk-Lock Back-Average analysis or Back-Average Analysis

K

KISS – keep it simple and straightforward

L

LFF – Low Frequency Filter

Ln – natural Logarithm

LPCE – Liga Portuguesa Contra a Epilepsia

M

MAC - Macintosh

MCA – Middle Cerebral Artery

MOOSE – Meta-analyses Of Observational Studies in Epidemiology

mRS – Modified Rankin Scale

N

NA – Not Applicable

NCSE – Non-Convulsive *Status Epilepticus*

NIHSS – National Institutes of Health Stroke Scale

ns– non-significant

O

OR - Odds Ratio

P

PC – Patrícia Canhão

PD – Periodic Discharges

PRISMA – Preferred Reporting Items for Systematic review and Meta-Analysis

PRISMA-P – PRISMA Protocols

pTIA – Possible TIA

PROSPERO – International prospective register of systematic reviews

Q

qEEG – quantitative EEG

R

RAWOD – Regional attenuation without delta activity

rtPA – recombinant tissue-type plasminogen activator or alteplase

ROC – Receiver Operating Characteristic Curve

RP – Relative Power

RSWA – Rhythmic Slow Wave Activity

RR – Relative Risk

S

SAH – SubArachnoid Haemorrhage

SAMPL – Statistical Analyses and Methods in the Published Literature

SD – Standard Deviation

Secs – Seconds

SPECT – Single Photon Emission Computed Tomography

SPSS – Statistical Package for the Social Sciences

SWI – susceptibility-weighted brain magnetic resonance imaging

T

TIA – Transient Ischaemic Attack

TOAST – Trial of Org 10172 in Acute Stroke Treatment

U

US – Unprovoked Seizure(s)

USA – United States of America

V

V-EEG – Video-EEG monitoring

CONTENTS

I. INTRODUCTION

“Start by doing what's necessary;
then do what's possible;
and suddenly you are doing the impossible”
S. Francisco de Assis

1. RESEARCH TOPIC IMPORTANCE AND KNOWLEDGE GAPS SYNOPSIS

The electroencephalogram (EEG) is a neurophysiological technique with high temporal resolution and sensibility in the evaluation of brain function in real time. Besides, EEG is the *gold standard* for identifying different epileptogenesis and ictogenesis biomarkers[4,5]. Moreover, EEG does not have relevant contraindications, and is a painless exam that can be done at the patient's bedside, repeatedly or continuously, according to the clinical evolution without increased risks. It is also a low-cost exam, available in most hospitals. First used in humans in 1929 by Hans Berger[6], EEG survived rapid technological advances of brain imaging technics arising mainly in the 70s[7], and evolved including different technical modalities of recording and analysis of bioelectrical cerebral activity. Therefore, it progressively increased its importance in the diagnosis, treatment programing and evaluation and also in functional prognostication of specific neurological disorders. Currently, it is frequently used in Neurology clinical practice as a complementary technique to the essential clinical assessment of brain function, either alone or in a multimodal perspective[7]. In fact, EEG is an essential neurophysiological exam in the evaluation of patients with epileptic seizures, *status epilepticus* and/or epilepsy, both for diagnosis and classification, as well as for the establishment of a correct treatment[3,8]. Furthermore, EEG has been used in cerebrovascular disease with different clinical and research purposes (described in detail in introduction point 2). However, the clinical usefulness of this neurophysiological technique in the differential diagnosis of transient neurological symptoms (namely in the differentiation between a transient ischaemic attack and some types of epileptic seizures) and also in the diagnosis or prediction of post-stroke seizures or even in stroke prognostication remains uncertain.

Cerebrovascular disease and epileptic seizures are two of the most frequent neurological disorders[9] being associated to different mutual challenges and relationships in clinical practice (expanded topic of introduction point 3).

The first clinical challenge is the differential diagnosis[10–16]. Although expert clinical assessment and cerebral imaging are undoubtedly useful, there is still a need for complementary diagnosis tools in helping this distinction[17]. However, there are few studies[18] about the EEG's value in the discrimination of these neurological entities.

Secondly, cerebrovascular disease is a frequent risk factor for epileptic seizures[19], accounting for more than half of all cases of epilepsy in elderly patients[20]. However, reported frequency of post-stroke seizures after an ischaemic stroke is variable (2-67%)[21–26] possibly due to different study methodologies including the lack of an electroencephalographic record[27]. Furthermore, in recent years, stroke care has evolved remarkably and facing a new paradigm of acute standard care (centred on multidisciplinary Stroke Units), epileptic seizures (as stroke complications) deserve to be rethought. As a matter of fact, intravenous alteplase (rtPA), the *gold standard* treatment for acute ischaemic stroke, has been associated with clinical seizures and the occurrence of epileptiform activity in the EEG[28,29]. It has even been documented that seizures during rtPA perfusion can occur even in the absence of a cerebral lesion, as described in 2 patients submitted to thrombolysis for acute myocardial infarction[30]. In fact, neurotoxic and epileptogenic properties[31] of rtPA are known. Other postulated mechanisms for seizures during thrombolysis for ischaemic stroke include secondary cortical infarct from distal embolization or reperfusion/hyperperfusion syndrome[32]. A different imaging pattern of the infarct in patients treated with rtPA might also predispose to seizure occurrence. Despite the clinical relevance of these observations, rtPA related seizures[30,32,33] and the frequency of seizures in patients treated with rtPA[34,35] has been mostly described in a few retrospective and non-controlled case series. Furthermore, it is known that clinical stroke severity and infarct dimension are risk factors for post-stroke epileptic seizures and vascular epilepsy[27] and that EEG is a sensitive neurophysiological technique in the detection of acute cerebral ischaemia[36] and a robust one in the functional assessment of the brain[37]. However, it is unclear whether electroencephalographic markers of acute vascular injury severity are independently associated with an increased risk of post-stroke seizures or useful for their prediction.

The third interaction between cerebrovascular disease and epileptic seizures is a possible outcome influence. Stroke is a leading cause of disability and mortality worldwide and global stroke burden is expected to rise in the future[38]. Despite the existence of demographic, clinical and imaging[27,39–42] predictors of stroke functional outcome, there is large interindividual variability in short and long-term outcome of ischaemic stroke[43] and still the need to identify reliable, inexpensive biomarkers that can add prognostic information in these patients. Post-stroke seizures[44,45] (and also electrographic seizures and interictal epileptiform discharges in critically ill patients[46–48]) have been associated to an unfavourable functional outcome of stroke patients. However, it is not known if this association is independent from stroke severity. Furthermore, due to accumulating evidence regarding

neuro-vascular uncoupling in acute ischaemic stroke, neurophysiological biomarkers seem increasingly relevant for predicting outcome[49].

We thought this project could expand the knowledge both about the EEG's value as a complementary neurophysiological tool and regarding two of the most prevalent neurological disorders, specifically regarding their differential diagnosis, the frequency and prediction of post-stroke epileptic seizures and epilepsy, and the influence of seizures and EEG abnormalities in stroke outcome.

2. THE EEG IN ISCHAEMIC CEREBROVASCULAR DISEASE

The recording and monitoring of EEG in patients with acute ischaemic cerebrovascular disease has been done in different contexts and is based on various types of evidence, which are described in the following paragraphs.

2.1. The EEG in the differential diagnosis of a Transient Ischaemic Attack (TIA)

The use of EEG in clinical models of TIA has been poorly explored. However, De Reuck & Van Maele[50] showed the importance of the EEG in the differential diagnosis of a TIA versus an inhibitory epileptic seizure. Comparing clinical and EEG features of patients with TIA and patients with inhibitory epileptic seizures, they found differences in age, sex and cerebrovascular risk factors between the two groups. In addition, most patients with seizures had EEG abnormalities (specific and nonspecific), while 90% of patients with TIA had a normal EEG. Furthermore, in a subgroup analysis (TIA with symptoms lasting less than 24 hours versus less than 1 hour) the clinical differences previously found were not significant, but (regardless of TIA definition) EEG findings remain different between TIA and epileptic seizures patients. The authors conclude that an urgent EEG is essential in the investigation of a transient episode of neurological dysfunction. In fact, EEG differences appeared to be larger than those found when comparing patients with and without unprovoked seizures after stroke[51]. This evidence increased the number of EEG requests for patients admitted to the TIA Clinic of our Neurology Department, especially in patients with difficult-to-diagnose transient neurological symptoms or possible TIA. However, the type and frequency of EEG abnormalities in possible TIA and their value in the distinction between an epileptic seizure and a TIA is not exactly known.

2.2. The EEG in the detection of acute cerebral ischaemia

EEG abnormalities are early markers of cerebral ischaemia and reflects the disturbance of oxygen metabolism[52] and the reduction of cerebral blood flow[53,54]. The first EEG changes occur when cerebral blood flow reaches 25-30 ml/100g/minute. At this level, therapeutic interventions may prevent brain damage which is established for flows lower than 18 ml/100g/minute[55–57] and reversible until a flow of 12ml/100g/minute[36]. Mild hypoxia (cerebral blood flow of 25-30 ml/100g/min) determines a subtle reduction of the amplitude

of rapid activity (>13 Hz) in the EEG. The worsening of ischaemia results in the appearance of polymorphic delta activity and more marked attenuation of rapid activities, including alpha and sleep spindles[58,59]. The use of quantitative EEG (qEEG) also showed a relationship between focal ischaemia and some indices such as the absolute and relative power of different spectral bands[58,60,61] and brain symmetry index[62].

Given the availability and characteristics of current cerebral imaging techniques, EEG is not currently used for the diagnosis or for the topographical location of an ischaemic stroke. However, some EEG patterns such as regional attenuation without delta (RAWOD)[63] have been suggested as possible support for patient selection in the emergency department for thrombolysis or treatment of cerebral oedema[64]. In fact, some authors agree that EEG can be used in an acute stroke setting as a continuous monitor of cerebral perfusion to detect progressive or recurrent ischaemia[59].

2.3. The EEG in the detection of revascularization and ischaemic stroke treatments effects

The EEG is sensitive to cerebral reperfusion and can demonstrate recovery earlier than the clinical examination[65]. This observation makes it a potentially very useful tool for continuously monitoring cerebral perfusion and stroke revascularization therapy. In fact, EEG monitoring was classically performed during endarterectomy[36,66]. This technique demonstrated that cerebral reperfusion is associated with neurophysiological abnormalities including changes in the EEG background activity frequency and amplitude and even epileptiform activity. EEG changes are not exclusive to endarterectomy. In fact, several other studies showed EEG changes associated with different ischaemic stroke treatments:

- Focal EEG slowing normalized when regional cerebral blood flow was elevated above the ischaemic threshold after hypervolaemic and hypertensive therapy[67].
- There was a correlation between the percentage of theta and delta activity in relation to total activity (qEEG) and cerebral blood flow measured by single photon emission computed tomography (SPECT), before and after isovolaemic haemodilution in patients with middle cerebral artery stroke[68]
- There was a good correlation between topographic maps based on qEEG parameters and control of blood pressure in atherosclerotic acute stroke patients[69].
- An improvement in acute delta change index (ADCI) and National Institutes of Health Stroke Scale[70] (NIHSS) score was observed in the only patient of the Finnigan et al.[71] study

treated with intravenous thrombolysis. According to the authors, this favourable clinical evolution would not be suspected based on acute MRI.

- A relationship was demonstrated between NIHSS score and brain symmetry index (BSI)[62], in 16 patients undergoing intravenous thrombolysis. Van Putten and collaborators suggested that abnormalities of this qEEG index could alert the clinician to re-examine the patient, detecting early clinical abnormalities.

Despite these evidences, and the fact that intravenous thrombolysis[72] (sometimes followed by mechanical thrombectomy) is now the gold standard treatment for acute ischaemic stroke, there is no large prospective study, using EEG monitoring during or after thrombolysis. Claassen & Hirsch[73] further suggested that monitoring may also be used in hospitalized patients at high risk of stroke after TIA[74] for early detection of ischaemia and maximize the benefit of thrombolysis.

2.4. The EEG in the detection of epileptiform activity after ischaemic stroke

Seizures and *status epilepticus* often occur after acute brain injury. In an intensive care environment, seizures are mainly electrographic and therefore cannot be detected merely by clinical observation. Claassen and colleagues[75], in a series of neurological patients admitted to an Intensive Care Unit (ICU) and submitted to continuous EEG monitoring showed that 19% had seizures, mostly (92%) without obvious clinical manifestations. EEG monitoring is also essential in the diagnosis and treatment of *status epilepticus* in a neurological ICU[46]. One type of acute brain injury is ischaemic stroke and it is known that among these patients, those with clinical indication for continuous EEG monitoring, 11% will have seizures[36,76], 9% exclusively non-convulsive seizures and 7% criteria for the diagnosis of non-convulsive *status epilepticus*[75]. Furthermore, a prospective study [29] using EEG monitoring showed that 17% of acute ischaemic and haemorrhagic stroke patients have epileptiform activity but the time interval between stroke and EEG and the record duration time (between 1 and 37 hours) were not predictors of that occurrence. Therefore, the optimal duration of an EEG record to detect epileptiform activity after stroke is still to be defined. Moreover, in the study of Carrera and collaborators[29], factors that significantly increased the likelihood of EEG epileptiform activity were: NIHSS score on admission, cortical involvement and intravenous thrombolysis. However, in multivariate regression analysis, only the NIHSS score was an independent predictor. In fact, this study included 100 patients but only 11 were treated with intravenous thrombolysis (4 of whom had epileptiform activity in the EEG). Therefore, a

conclusion about the epileptogenic effect of rtPA could not be inferred. However, it is suggested that patients undergoing this treatment, particularly those with secondary clinical worsening, should have a tight EEG follow-up to exclude electrographic seizures. In animal models tissue plasminogen activator may facilitate seizures[77] and has been implicated in epileptogenesis[78]. Nevertheless, the relationship between intravenous alteplase and clinical seizures is not established. There are studies suggesting an association of acute symptomatic seizures and intravenous thrombolysis[28] but De Reuck and Van Maele[32], comparing the occurrence of seizures in patients treated and or not treated, showed that early seizures were related to stroke severity and late seizures tended to be lower in the treated group. Furthermore, the influence of seizures in the outcome of ischaemic stroke patients submitted to intravenous thrombolysis is also a matter of discussion. Some studies suggest that seizures during thrombolysis represent reperfusion and neurological recovery[32] whereas others indicate a potential negative influence of seizures on clinical outcome of thrombolysed stroke patients[28].

2.5. The EEG in the prediction of ischaemic stroke outcome

Seizures, *status epilepticus* and EEG abnormalities have been associated with an unfavourable stroke outcome[44,45,64,71,79–89]. Nevertheless, it is questionable whether these features are markers of the extent of brain damage or even if they cause further brain injury. Regarding ischaemic stroke, several EEG features have been associated with an unfavourable outcome, including: EEG background slowing[85,86] and contralateral slowing[86]; polymorphic delta/theta, slowing of alpha or depressed beta activity, or both[87]; different qEEG indexes[89] including an increase in Acute Delta Change Index (ADCI)[71] and regional attenuation without delta activity (RAWOD)[64]. Sometimes qEEG abnormalities were better than clinical (using Canadian Neurological Scale)[89] or imaging investigation for the outcome prediction[71]. However, it is unknown whether the association between EEG abnormalities and stroke functional outcome is independent from already known cerebral infarct outcome predictors, namely age and stroke (clinical and imaging) severity[39–42].

In short, in ischaemic cerebrovascular disease, the EEG can potentially be used for the differential diagnosis of transient ischaemic events and, in acute stroke, as a cerebral perfusion monitor to detect progressive or recurrent ischaemia[59], to detect the presence of epileptiform activity, to monitor its therapy or even to predict its outcome[73].

3. INTERRELATIONS BETWEEN EPILEPTIC SEIZURES AND ISCHAEMIC CEREBROVASCULAR DISEASE

Epileptic seizures and cerebrovascular disease are two of the most frequent neurological disorders[9]. In addition to their high prevalence, these disorders share different biunivocal and bidirectional associations and relationships with some consequences for their own diagnosis, outcome and therapy. The following paragraphs describe these interrelations including differential diagnosis challenges, the causal relationship, mutual treatment interference, and outcome effects.

3.1. Differential diagnosis between an epileptic seizure and a TIA

One of multiple biunivocal relationships between epileptic seizures and cerebrovascular disease is the difficulty that can exist in their differential diagnosis. In both disorders transient focal neurological symptoms that can appear to be clinically similar are physiopathologically distinct.

3.1.1. Possible TIA and possible epilepsy

About a quarter of transient ischaemic attacks patients have "probable" or "possible" TIA[90,91], defined as a clinical syndrome lasting less than 24 hours that do not fulfil accepted criteria for TIA nor for another diagnosis, although a vascular origin cannot be excluded[91,92]. The main reasons for classification difficulties of possible TIA include odd accompanying symptoms (such as prickles/itching sensations, rigid postures or movement of the limbs), march of symptoms, consciousness disturbance or amnesia with focal symptoms, multiple stereotyped episodes, positive visual phenomena, isolated speech disturbance/confusion and focal symptoms plus panic or anxiety and paucity of details in the symptoms description[91]. Similarly, in the absence of a seizure documented by video-EEG recording and typical for the patient´s usual seizures, there will be situations where a diagnosis of epilepsy remains uncertain[93]. One approach to this difficulty is to consider uncertain cases as “probable” or “possible epilepsy”. The ILAE task force, aimed to formulate an operational definition of epilepsy for clinical diagnosis purposes[93], has indeed left that possibility open for the future.

3.1.2. Akinetic seizures and Todd´s phenomena as TIA mimics

It is true that epileptic seizure semiology is most frequently associated with positive symptoms. Nevertheless, negative ones (when occurring) may bring difficulties to the differential diagnosis with cerebrovascular events. In fact, electrical stimulation of the human cortex typically elicits positive sensorimotor effects although several cortical stimulation studies, since Penfield and Jasper[94] (1954), have also reported cortical areas in which stimulation produces inhibition or arrest of on-going movement[95]. These cortical regions are located laterally in the inferior frontal gyrus and premotor cortex and medially in the supplementary motor area (SMA) and pre-SMA[95,96]. In the dominant hemisphere, the dorsal negative motor area coincides with Broca´s area. Lüders and collaborators[97] named these cortical zones as “negative motor areas", and speculate their involvement in motor planning. Typical negative motor responses by electrical stimulation of these areas include speech arrest and arrest of movements of the hand, leg and foot without loss of awareness. Ikeda et al.[96] suggested that negative motor areas are indeed responsible for negative motor seizures, a rare epileptic condition that consists of motor arrest, inability to conduct voluntary movements or praxis, due to epileptic interference in a similar way to how it occurs in higher cortical areas (such as the language areas) where epileptic activation always produces inability of the functions (such as aphasia, but never creates spontaneous words or speech). Negative motor seizures should be distinguished from focal ictal paresis (or ictal atonia), linked to primary sensorimotor cortex inactivation[96]. Nevertheless this distinction is not always evident in literature [10,98–101] and is often difficult in clinical practice. It seems puzzling that the same cortical area (primary motor cortex) can produce positive and negative symptoms, that is, is capable of generating clonic and also atonic seizures. This phenomenon may be explained by the amount of cortex involved in the epileptic discharge[102], a phenomena that was named vertical restriction of focal seizure activity. Engel and Speckmann[103] showed that superficial epileptic foci and foci involving all layers of the cortex produce indistinguishable epileptiform discharge. However, only the focus involving all cortical layers was able to produce a spinal discharge and only spikes localized in the superficial layer produced sustained inhibitory activity in the deep layer. This may explain negative motor events when an epileptiform potential is recorded over the motor cortex.

Despite having different cortical generator mechanisms, clinically negative motor seizures and focal ictal paresis are rarely distinguished, since simultaneous EMG recording is often not performed. The diagnosis relies on either clinical testing for a movement task or detailed history after the event to determine whether the patient intended to perform movements. To

avoid nomenclature misunderstanding, some authors prefer to call these two seizure types (negative motor seizures and focal ictal paresis) as akinetic seizures referring to seizures with both lack of initiation of movement or paucity of movement secondary to muscle atonia[102].

In the De Reuck et al. study[18], speech disturbance was the most common presentation of inhibitory seizures occurring in more than 60% of elderly patients. Moreover, speech disturbances are one of the reasons for classification difficulties of possible TIA[91]. Different forms of speech disturbance can be observed in epileptic seizures including ictal speech arrest due to negative motor seizures and ictal aphasia arising in and involving language areas such as Broca's area[104], Wernicke's area[105] and basal temporal language area[106].

Post ictal paresis (Todd`s paralysis) lasting hours to days or other symptoms of Todd post-ictal phenomena including gaze palsy, hypoesthesia and aphasia[107] or even neglect and other neurocognitive focal deficits[108], can also trigger differential diagnosis problems with cerebrovascular disease, specifically with transient ischaemic attacks. This is so because an outside observer may not testify transient ictal positive symptoms preceding post-ictal deficits or the patient, due to aphasia, anosognosia, memory or consciousness impairment, might also not describe them. Various hypotheses about the mechanism of this post-ictal symptom have been proposed including exhaustive neuronal firing, desensitization and active suppression.

3.1.3. Limb-shaking TIA and other epileptic seizures mimics

Diagnostic challenges between a TIA and an epileptic seizure include not only non-convulsive, atonic and inhibitory or negative seizures[10–13,109,110] but also TIA with positive symptoms such as "limb-shaking" TIA, first reported by Miller Fisher[14] in 1962. In this entity, jerky involuntary movements involving an arm or leg can be recognized by their short duration and are often accompanied by paresis and precipitated by standing up or exercise[111]. Limb-shaking TIA is indicative of an impaired haemodynamic state of the brain and a manifestation of an intracranial and extracranial carotid occlusion or severe stenosis. Recently, Muraga[15] and collaborators described a patient with a "limb-shaking TIA" associated with intracranial carotid stenosis having jerk-locked back-average proven cortical myoclonus and suggested that ischaemia-induced neuronal hyperexcitability of the cerebral cortex was associated with contralateral shaking movements.

Further hampering the distinction between a TIA and an epileptic seizure is the possibility that epileptic seizures can be caused by a TIA[13,112,113] and the existence of other mimics with a non-vascular and non-epileptic origin[16].

3.1.4. The particular case of amyloid spells

Sporadic cerebral amyloid angiopathy is a common age related cerebral small vessel disease. It is characterised by progressive deposition of amyloid-β in the wall of small to medium sized blood vessels of the brain and leptomeninges[114]. Although usually asymptomatic, it is an important cause of primary intracerebral haemorrhage in the elderly. In addition to the typical lobar (cortical or cortical-subcortical) haemorrhage, various types of abnormal imaging features might also be found in this pathological condition, such as, lobar microbleeds, convexity subarachnoid haemorrhage, cortical superficial siderosis, microinfarction and leukoaraiosis[115,116].

The clinical spectrum of sporadic cerebral amyloid angiopathy include not only focal neurological deficits due to lobar (especially occipital and temporal) intracerebral haemorrhage in older individuals (generally over 55 years) but also cognitive impairment, dementia, and transient focal neurological symptoms[117–119], frequently called “amyloid spells”.

Amyloid spells have been described as recurrent, stereotyped and transient episodes of ‘positive’ spreading sensory symptoms (paraesthesias) into contiguous body areas[118]. However, positive ("aura-like") and negative symptoms ("TIA-like", such as focal weakness and dysphasia) appear to be equally common (52% vs. 48%, respectively)[116]. Therefore, clinically, amyloid spells might resemble TIA, migraine aura or even seizures[120] and should be included in the differential diagnosis of those conditions, especially in adults over 55 years.

Amyloid spells are probably more often related to bleeding into the brain (especially superficial cortical siderosis, convexity subarachnoid haemorrhage and lobar cerebral microbleeds) rather than ischaemia[116,120]. For that reason, blood-sensitive magnetic resonance imaging sequences, including T2*-weighted gradient-recalled echo (T2*-GRE) and susceptibility-weighted imaging (SWI) should be included in the investigation of such episodes. In fact, in Andreas Charidimou et al. multicentre cohort[116] transient focal neurological episodes were strongly associated with cortical superficial siderosis likely resulting from repeated bleeding into the subarachnoid space and subsequent deposition of hemosiderin in the superficial (subpial) cortical layers. Physiopathologically, it remains

unclear whether amyloid spells are related to cortical spread depression, to an epileptic process, to both (together or sequentially), or if these two mechanisms operate differently in different amyloid related cerebral lesions. In line with this concept, both antiepileptic drugs and migraine prophylaxis[121] have been suggested for symptomatic treatment of these transient neurological symptoms.

The diagnosis of amyloid spells is important due to the fact that they seem to predict a high early risk of symptomatic intracerebral haemorrhage (about 50% at two to three-months)[116]. Furthermore, their misinterpretation with TIA associated with the prescription of antiplatelet agents[122] or anticoagulation[123,124] is likely to increase the risk of haemorrhage.

3.1.5. Ancillary investigation and differential diagnosis between an epileptic seizure and a TIA

An acute ischaemic lesion in diffusion-weighted brain Magnetic Resonance Imaging (DWI) can be used in clinical practice in this differential diagnosis. However, this exam demonstrates an acute ischaemic lesion in only 30% to 50% of TIA patients, depending on the additional performance of a perfusion-weighted study[125]. In addition, the proposed paradigm shift in the TIA definition[126,127] might increase the differential diagnosis difficulty between a TIA and an epileptic seizure. If the TIA definition based on the duration of the clinical event ("time-based") is changed to the absence of an ischaemic lesion ("tissue-based"), both conditions (a TIA and an epileptic seizure) are characterized by the absence of an acute ischaemic lesion. Therefore, this shift enhances the need for other complementary strategies for this important neurological differential diagnosis. On the other hand, epileptic seizures[128,129] and *status epilepticus*[130–132] have also been associated with evanescent diffusion-weighted imaging abnormalities mimicking those of a transient ischaemic attack. In fact, Lansberge[130] et al. described cortical hyperintensity on DWI and T2-weighted sequences and a corresponding area of low apparent diffusion coefficient in complex partial *status epilepticus* patients. However, these findings were readily differentiated from typical ischaemic stroke in their nonvascular distributions, an increased signal of the ipsilateral middle cerebral artery on magnetic resonance angiography, and leptomeningeal enhancement on post contrast magnetic resonance imaging.

Perfusion CT scan has also been described as a possible differential diagnosis tool between cerebrovascular disease and stroke mimics including inhibitory seizures, ictal or post-ictal paresis (Todd`s paralysis)[133–135]. Seizures have been demonstrated to cause an increase in

cerebral blood flow and cerebral blood volume in the acute phase, likely due to a vasodilatory response to the increased metabolic demands of ictal activity. However, the results of this exam depend on the time from the beginning of ictal symptoms (transient by nature) as an hypoperfusion pattern on perfusion CT has also been described[136,137].

The EEG and its related techniques are the gold standard for the identification of epileptogenesis and ictogenesis biomarkers[4,5]. Therefore, it is plausible that it can be useful in the differential diagnosis between epileptic seizure and TIA. However, clinical evidence about the application of this neurophysiological test is quite limited and is restricted to the results of a single workgroup[50].

3.2. Seizures as a consequence of cerebrovascular disease

3.2.1. Post-stroke seizures/epilepsy frequency

The most obvious connection between epileptic seizures and cerebrovascular disease is perhaps the possibility of the former being a consequence of the latter. Epilepsy patient cohorts reveal a high frequency of vascular epilepsy. A systematic review of epilepsy epidemiology in Europe[138] showed that the most common aetiology for epilepsy was cerebrovascular disease (ranging from 14-21%), especially ischaemic stroke (16-18%). In fact, cerebrovascular disease is the most common cause of acquired epilepsy[19] corresponding to 22% of epilepsy in adults and 55% of *de novo* seizures in the elderly[139]. Thus, with the expected average longevity increase, the prevalence of post-stroke seizures and vascular epilepsy may increase.

The frequency of post-stroke seizures and epilepsy is quite different in cerebrovascular disease patient studies, varying between 2 and 67%[21–26], possibly due to different study methodologies, such as the prevalence of different types of stroke and stroke lesions in a given study population. In fact, different post-stroke seizures and epilepsy risk factors have been identified[27,140,141]. Haemorrhagic stroke, haemorrhagic transformation of an infarct, cortical involvement and stroke severity are among the most important risk factors for post-stroke seizures and epilepsy[140,141]. Furthermore, different post-stroke seizures and epilepsy definitions have been used in different studies, certainly affecting frequency analysis. To overcome this problem in future studies, the International League Against Epilepsy (ILAE) has published recommendations for seizure type definition[142] in relation to acute and remote cerebral lesions. Furthermore, the definition of epilepsy has been recently adjusted[93],

theoretically modifying the incidence and prevalence of epilepsy, especially in studies with a short follow-up time.

Another factor that has been reported as contributive to the discrepancy in post-stroke seizures frequency analysis is the absence of EEG in most studies[27]. In patients with acute neurological injury the majority of seizures are electrographic[75]. Therefore, in the absence of a neurophysiological study the frequency of seizures may be underestimated, even in patients who do not require hospitalization in intensive care units.

Other caveats to the interpretation of clinical data related to post-stroke seizures frequency include accuracy of stroke diagnosis, follow-up duration, sample size and heterogeneity of study designs, use of univariate versus multivariate statistics for data analysis, availability and analysis of CT and MRI scans for diagnosis and follow-up, accuracy regarding the localization and type of primary lesion, and the use of drugs and other medications acutely or during follow-up[27].

3.2.2. Post-stroke seizures/epilepsy definitions, physiopathology and clinical implications

Epileptic seizures can occur with different temporal associations with stroke and distinctive physiopathological mechanisms have been proposed for their occurrence[21,143]. Seizures occurring in the first 7 days after stroke[142] are considered acute symptomatic seizures and are thought to result from cellular biochemical dysfunction and local metabolic disturbances (and not necessarily altered neuronal networks) leading to electrically irritable tissue. Possible physiopathological mechanisms parallel those of acute ischaemic lesion and include glutamate excitotoxicity, accumulation of intracellular calcium and sodium with depolarization of the transmembrane potential and other calcium-mediated effects lowering seizure threshold[144]. In contrast, occurrence of post-stroke unprovoked seizures[145] or seizures after that time point[44,142,145] have been associated with different physiopathological mechanisms including inflammation and remodelling of synaptic networks leading to gliosis, development of a meningocerebral cicatrix and brain acquisition of an enduring predisposition to generate epileptic seizures, conceptually defining epilepsy[146]. This insult-induced process where a cascade of changes transforms the nonepileptic brain into one that generates spontaneous recurrent seizures is called epileptogenesis. Traditionally, a latent period between stroke and the development of symptomatic acquired epilepsy has been described. However, a different concept has also been proposed[147] with epileptogenesis and often subclinical epilepsy starting immediately after brain injury without any appreciable latent period[147], based on recent data from both animal models and clinical studies. The risk

of epileptogenesis after stroke is most likely influenced by injury severity, location and type of pathological changes, genetic factors and also pre-injury and post-injury exposure to non-genetic factors (i.e., the exposome)[27]. In fact, hyperglycaemia, diabetes, dyslipidaemia, hypertension, cardiovascular morbidities, peripheral infections, early seizures, haemorrhagic transformation, depression, use of antidepressants, use of statins, and pre-existing dementia might modulate post-stroke epileptogenesis[27].

Although the 7 days cut-off time-point for differentiation between acute symptomatic seizures and unprovoked seizures has been considered arbitrary[27] (and, therefore, not consensual), it is biologically plausible as it is associated with a different seizure recurrence risk. In fact, the risk of subsequent unprovoked seizure after 10 years of follow up is 33.0% (95% CI = 20.7-49.9%) for those who experience a first acute symptomatic seizure within 7 days of the stroke onset and 71.5% (95% CI 59.7-81.9%) for first unprovoked seizure after stroke[44]. For this reason, this 7 days cut-off time-point is clinically very important as it implies that a patient with one unprovoked seizure after stroke has epilepsy[93] and therefore antiepileptic drug therapy should be considered[148]. This is a new concept in epileptology[93]. Epilepsy was defined conceptually in 2005[146], as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition was usually practically applied as having two unprovoked seizures more than 24 h apart. However, the “two unprovoked seizure” definition of epilepsy was inadequate in some circumstances, such as in patients with brain insults, which have a comparable risk of a second or a third unprovoked seizure. Consequently, the ILAE commissioned a task force to formulate an operational definition of epilepsy for purposes of clinical diagnosis, published by Fisher et al. in 2014[93]. This new definition includes “one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years”. The 60% value was selected as it is the 95% confidence interval inferior value of the recurrence risk of the first acute symptomatic seizure after stroke[44].

3.3. Seizures, a biomarker of cerebrovascular disease

After 60 years of age, 5-20% of incident cases of seizures or epilepsy can herald stroke[149]. The term heraldic seizures has been used for epileptic seizures caused by silent ischaemia and occurring before a clinical stroke[150,151]. As a marker of subclinical vascular disease, seizures can in this context be considered biomarkers of cerebrovascular disease.

Cleary et al. study[152] revealed that the onset of seizures at or after the age of 60 in patients without a history of cerebrovascular disease, other acquired brain injury, brain tumour, drug or alcohol misuse, or dementia is associated with relative hazard of stroke of 2.89 (95% CI 2·45-3.41) compared to randomly selected matched controls with no history of seizures. These authors comment that this relative hazard can be compared with the relative risk of 1.46 associated with low HDL-cholesterol concentrations[153] and is the doubling of the risk associated with smoking[154,155]. Furthermore, Maxwell and collaborators[156] investigated the prevalence of radiological cerebrovascular disease in late onset epilepsy patients showing that small vessel disease (periventricular or subcortical white matter lesions, including leukoaraiosis) is more prevalent in patients than in controls matched for age, gender and type of brain imaging. Another interesting finding is that different ictal onset zones seem to be associated to different types of radiologic cerebrovascular disease. While in patients with post-stroke epilepsy and a well-defined vascular lesion, epileptogenic focus was coherent with it, in patients with leukoaraiosis temporal lobe epilepsy predominated. Although a casual relation or the occurrence of cortical microinfarcts could not be excluded, the authors discuss hypothetical leukoaraiosis-induced damage to temporal lobe networks.

Also, a systematic review[157] suggests that patients with seizures occurring for the very first time in late life and without clinically overt cerebrovascular disease should be considered as having an increased risk of stroke and be screened for the presence of vascular risk factors.

3.4. Seizures and the current acute stroke standard of care

Acute stroke care has change tremendously in recent years. Stroke patients who receive organised inpatient care in multidisciplinary teams that manage stroke patients in a dedicated ward are more likely to be alive, independent, and living at home one year after the stroke[158,159]. Currently, it is recommended that all stroke patients are treated in a Stroke Unit (Class I, Level A recommendation[72]). Furthermore, long-term survival[160] and outcome[161] improved in patients receiving intravenous thrombolysis. However, it is unclear what the impact is of intravenous alteplase (rtPA) on the frequency of post-stroke seizures.

Some lines of evidence, from basic science and clinical research[28,29,31,32,77,78,162,163], suggest that alteplase may have a proconvulsive and even an epileptogenic effect. Also, the survival of islands of cortical viable tissue[164] have been described in patients with post-stroke epileptic seizures[165]. Furthermore, the "stunned brain" syndrome[166,167], theoretically, might also contribute to a higher risk of epileptic events. In fact, clinical response immediately

after revascularisation therapy differs among patients and almost 40% of non-responsive alteplase treated patients still achieved good outcomes at 3 months, suggesting the possibility of a "stunned brain" syndrome with delayed recovery[166,167]. This syndrome can be described as a state where the brain is temporarily and reversibly “stunned” by the ischaemic insult[168] paralleling the “stunned myocardium”[169] or post ischaemic myocardial dysfunction characterized by a prolonged contractile depression after alleviation of severe ischaemia by reperfusion of coronary occlusion. At least in part, this contractile dysfunction can be viewed as a form of "reperfusion injury"[170]. Cardiac reperfusion arrhythmias have also been described as marker of flow restoration during intracoronary thrombolysis for acute myocardial infarction[171] and several different mechanisms may potentially account for the "stunned myocardium" and also for reperfusion arrhythmias. The two major hypothesis are that it is caused by the generation of oxygen-derived free radicals (oxyradical hypothesis) and by a transient calcium overload (calcium hypothesis) on reperfusion[170]. Curiously, the cascade of events described in reperfusion heart dysfunction is similar to that suggested for reperfusion related cerebral injury and cerebral hyperperfusion syndrome. In fact, seizures as a manifestation of cerebral reperfusion injury after administration of intravenous alteplase[30], have been described.

On the other hand, the reduction of clinical severity and infarct size associated with intravenous alteplase may influence the occurrence of seizures exactly in the opposite direction. Intravenous alteplase related seizures[30,32,33] and seizure frequency in patients treated with alteplase[34,35] has been mostly described using retrospective and non-controlled case series. The hypothesis that treatment with alteplase may influence the prevalence of post-stroke seizures remains unanswered.

Furthermore, seizures after stroke have been associated with an unfavourable outcome in a few clinical studies on rtPA effect in functional outcome in the subgroup of patients treated with intravenous alteplase. Vincent Alvarez et al.[28] found that alteplase treated patients with post-stroke seizures have an unfavourable functional outcome at three months. In Gensicke and collaborators study[172], seizures were also independent predictors of long term poor outcome in rtPA treated patients. However, it is not known if outcome is different in patients with seizures treated and not treated with alteplase.

3.5. Prediction of seizures in cerebrovascular disease

Seizures and cerebrovascular disease are both known causes of neurological disability[38]. Furthermore, the occurrence of seizures seems to be associated to a lower quality of life in older patients with an ischaemic stroke[173]. Therefore, knowledge of post-stroke seizure predictors may have a high clinical impact. Already known predictors of seizures after ischaemic stroke include clinical and imaging stroke severity and its cortical involvement[25,174,175]. Although EEG is a sensitive neurophysiological technique in the detection of acute cerebral ischaemia[36] and a robust one in the functional assessment of the brain[37], it is unclear whether electroencephalographic markers of acute vascular injury severity are independently associated with an increased risk of post-stroke seizures or useful for its prediction. Furthermore, epileptogenic zone and cortical hypersynchronisation neurophysiological biomarkers, and its independence from already known risk factors for post-stroke seizures have not been explored, again, by the lack of prospective electroencephalographic records in most studies.

The search for a reliable biomarker or, more likely, a profile of biomarkers[176] of epileptogenesis and ictogenesis that could predict who has or will get epilepsy is of utmost clinical relevance, allowing a more personalized Medicine and Neurology care and increasing the feasibility of an eventual antiepileptic drug trial after stroke[175], in the future.

3.6. Seizures and the outcome of cerebrovascular disease

The possibility emerged in the literature of an association between post-stroke seizures (and *status epilepticus*) and the functional outcome of stroke[44,45,79–83]. However, the question remains whether this association is independent from other known prognostic factors of cerebrovascular disease. Furthermore, although the EEG is essential for the detection of interictal and ictal epileptiform activity, it is unknown whether the presence of these electroencephalographic activities is also associated to post-stroke functional outcome.

3.7. Other interrelationships between seizures and cerebrovascular disease

Different pharmacological therapies can affect both seizures and cerebrovascular disease. Statin therapy has been widely used in the prevention of stroke for many years and associated not only with a favourable outcome at stroke onset[177], but with a reduced risk of early post-stroke seizures[178] and hospitalization for epilepsy[179]. Furthermore, some antiepileptic drugs can affect vascular risk factors[180] including serum lipid profile[181,182] and interact with different stroke treatments as anticoagulants and other cardiovascular medications[183,184]. Besides, since AED work by modulating neuronal signalling (suppressing neuronal excitability or enhancing inhibitory neurotransmission) they often lead to cognitive and behavioural deficits[185] and also to psychiatric effects[186], with the risk of inducing or worsening co-morbidity in cerebrovascular patients. As a matter of fact, for the management of stroke-related seizures, no single antiepileptic drug was found to be more effective over others, though newer AEDs were associated with fewer side effects[187]. Furthermore, some AED have been demonstrated to impair functional recovery after stroke in the animal model [188] and in patients with intracranial haemorrhage[189].

Another challenge between cerebrovascular diseases and epilepsy is the task of prevention. Although the incidence of epilepsy in those younger than 65 years has not changed in the last 40 years, epilepsy in the elderly population has increased 5-fold[190] meaning that prevention of epilepsy includes certainly the improvement of care to prevent and treat cerebrovascular disease.

II. AIM OF THE STUDY

"Setting goals is the first step in turning the invisible into the visible"

Tony Robbins

In this work, the aim was to use the clinical model of acute ischaemic cerebrovascular disease (transient and established) to study the value of EEG in the differential diagnosis of transient neurological symptoms namely possible TIA, in the diagnosis and prediction of post-stroke seizures (and EEG epileptiform activity), as well as to analyse if EEG abnormalities and epileptic seizures are independent predictors of anterior circulation ischaemic stroke outcome.

III. RESEARCH QUESTIONS and RESEARCH OUTLINE

"This is a good question.
I once learned that a good question is greater than the most brilliant answer"
Louis Kahn

The following research questions drove different research projects, as displayed in the research projects outline (**Table 1**):

Question 1. What is the frequency of electroencephalographic abnormalities in patients with possible TIA and to which clinical/imaging characteristics are they associated?

Question 2. What is the percentage of patients with possible TIA having a final diagnosis of epileptic seizure or definitive TIA and which electroencephalographic characteristics differentiate these diagnoses?

Question 3. What is the frequency of post-stroke EEG epileptiform activity, both ictal and interictal in observational studies?

Question 4. Is the frequency of electrographic and clinical seizures different in stroke patients admitted to a Stroke Unit?

Question 5. What is the frequency of *epilepsia partialis continua* as a remote stroke complication?

Question 6. Are involuntary movements observed during intravenous alteplase perfusion of cortical origin?

Question 7. Is the frequency of seizures and electroencephalographic abnormalities different between stroke patients treated and non-treated with rtPA?

Question 8. Are early electroencephalographic abnormalities independent predictors of post-stroke epilepsy?

Question 9. Which are the predictors of EEG epileptiform activity in acute ischaemic stroke?

Question 10. Are seizures and early electroencephalographic abnormalities independent predictors of stroke functional and vital outcome?

Question 11. Are qEEG abnormalities independent predictors of stroke functional outcome?

Question 12. Is qEEG superior to visual analysis in the prediction of stroke functional outcome?

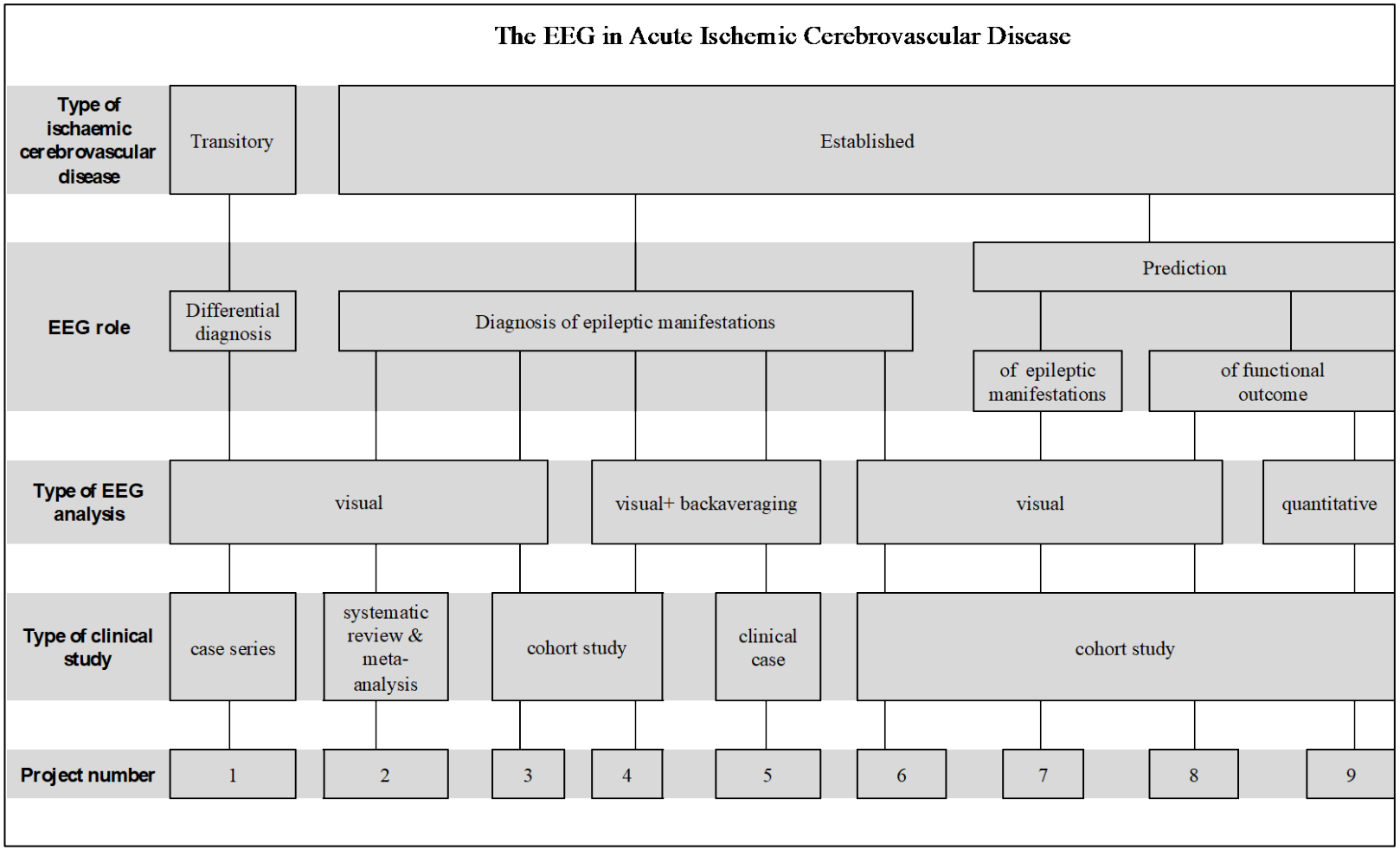
Table 1. Research projects outline

	Ischaemic Cerebrovascular Disease	
Type of event: Aim of the EEG:	TIA	Stroke (anterior circulation)
Differential Diagnosis	Question 1 and 2 Project 1	Question 6 Project 5
Post-Stroke Seizures (and EEG epileptiform activity) Diagnosis	-	Question 3, 4, 5 and 7 Project 2, 3, 4, and 6
Post-stroke Seizures (and EEG epileptiform activity) Prediction	-	Question 8 and 9 Project 7
Stroke Outcome Prediction	-	Question 10, 11 and 12 Project 8 and 9

The projects included in this thesis were planned to study not only different types of ischaemic cerebrovascular disease using EEG with distinctive purposes but also diverse types of EEG analysis and clinical study designs (**Figure 1**).

All projects have been already submitted to international peer-review magazines and most of them published (**Table 2**).

Figure 1. Research project characteristics



Legend to figure 1: Epileptic manifestation - post-stroke seizures and/or EEG epileptiform activity; distinction of case series and cohort studies is based on Dekkers et al.[191]

Table 2. Research projects titles and status

Project number	Project title	Project status
1	Usefulness of EEG for the differential diagnosis of possible transient ischaemic attack	Published in Clinical Neurophysiology Practice (1st online: 18/10/2017)
2	Frequency of post-stroke epileptiform activity - a systematic review and meta-analysis of observational studies	Register in PROSPERO 2015 (CRD42015029362) Published in European Stroke Journal (1st online: 16/09/2017)
3	Post-stroke seizures are clinically underestimated	Published in Journal of Neurology (1st online: 14/08/2017)
4	*Epilepsia Partialis Continua* after an anterior circulation ischaemic stroke	Published in European Journal of Neurology (1st online: 12/05/2017)
5	Cortical myoclonus during IV thrombolysis for ischaemic stroke	Published in Epilepsy and Behaviour Case Reports (1st online: 16/10/2014)
6	Epileptic manifestations in stroke patients treated with intravenous alteplase	Published in European Journal of Neurology (1st online: 18/04/2017)
7	Early EEG predicts post-stroke epilepsy	Published in Epilepsia Open (1st online: 07/03/2018)
8	Seizures, EEG abnormalities and outcome of ischaemic stroke patients	Published in Epilepsia Open (1st online: 23/08/2017)
9	Quantitative EEG and functional outcome following ischaemic stroke	Published in Clinical Neurophysiology (1st online: 21/06/2018)

IV. PROJECT 1

"One of the commonest problems in medicine
is the interpretation of transitory spells or attacks of central nervous system origin"
Charles Miller Fisher (1913-2012)

USEFULNESS OF EEG FOR THE DIFFERENTIAL DIAGNOSIS OF POSSIBLE TRANSIENT ISCHAEMIC ATTACK

AUTHORS

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ABSTRACT

Objective: EEG value in possible transient ischaemic attacks (TIA) is unknown. We aim to quantify focal slow wave activity (FSWA) and epileptiform activity (EA) frequency in possible TIA, and to analyse its contribution to the final diagnosis of seizures and/or definitive TIA.

Methods: Prospective longitudinal study of possible TIA patients evaluated at a tertiary centre during 36 months and with 1-3 months follow-up. EEG was performed as soon as possible (early EEG) and one month later (late EEG). A stroke neurologist established final diagnosis after reassessing all clinical and diagnostic tests.

Results: 80 patients underwent an early EEG (45.8 hours after possible TIA): 52 had FSWA and 6 of them also EA. Early FSWA was associated with epileptic seizure or definitive TIA final diagnosis (p=0.041). Patients with these diagnoses had early FSWA (19/23; 82.6%) more frequently than EA (6/23; 26.1%). 6/13 (46.2%) patients with epileptic seizure final diagnosis had EA.

In the late EEG, 43 (58.1%) patients demonstrated persistent FSWA and 3 of them also EA. Persistent FSWA in the late EEG was more frequent in seizures than in TIA patients (91.7% vs. 45.5%). FSWA disappearance was associated with acute vascular lesion on neuroimage.

Conclusions: FSWA was the commonest EEG abnormality found in the early EEG of patients with possible TIA, but did not distinguish between TIA and seizure patients. In patients with seizures, FSWA was more common than EA and its persistence in the late EEG was more likely in patients with epileptic seizures than with TIA.

Significance: The majority of possible TIA patients with the final diagnosis of epileptic seizures do not have EA in the early or late EEG

KEY-WORDS

transient neurological symptoms, transient ischaemic attack, seizure diagnosis, epilepsy**,** epileptiform activity, focal slow wave activity

1. INTRODUCTION

Neurological syndromes lasting less than 24 hours include not only Transient Ischaemic Attacks (TIA) but also other clinical entities such as epileptic seizures. The differential diagnosis between a transient ischaemic attack (TIA), an epileptic seizure or other transient neurological disturbances can be challenging and depends on the clinician's expertise[90,91,192–195] and also on the available clinical information[90,91,196–198].

After extensive clinical investigation, approximately one-fourth of TIA patients are only labelled as "probable" or "possible TIA"[90,91], defined as a clinical syndrome lasting less than 24 hours that do not fulfil accepted criteria for TIA nor for another diagnosis, although a vascular origin cannot be excluded[91,92]. The main reasons for classification difficulties of possible TIA include odd accompanying symptoms (such as prickles/itching sensations, rigid postures or movement of the limbs), march of symptoms, consciousness disturbance or amnesia with focal symptoms, multiple stereotyped episodes, positive visual phenomena, isolated speech disturbance/confusion and focal symptoms plus panic or anxiety and paucity of details in the symptoms description[91].

Diagnostic challenges between a TIA and an epileptic seizure include non-convulsive and inhibitory or negative seizures[10–13] and TIA with positive symptoms, such as limb-shaking TIA[14,15]. Further hampering this distinction is the possibility of epileptic seizures caused by a TIA[13,112,113] and the existence of other mimics with a non-vascular and non-epileptic origin[16].

De Reuck and Van Maele[50] analysed the role of EEG in the differential diagnosis of a TIA versus an inhibitory seizure and concluded that an early EEG is crucial in their investigation. However, the type and frequency of electroencephalographic abnormalities in possible TIA and its value in the distinction between epileptic seizures and TIA is not exactly known. In this study we aim to respond to the following:

1) What is the frequency of electroencephalographic abnormalities in patients with possible TIA and to which clinical/imaging characteristics are they associated?

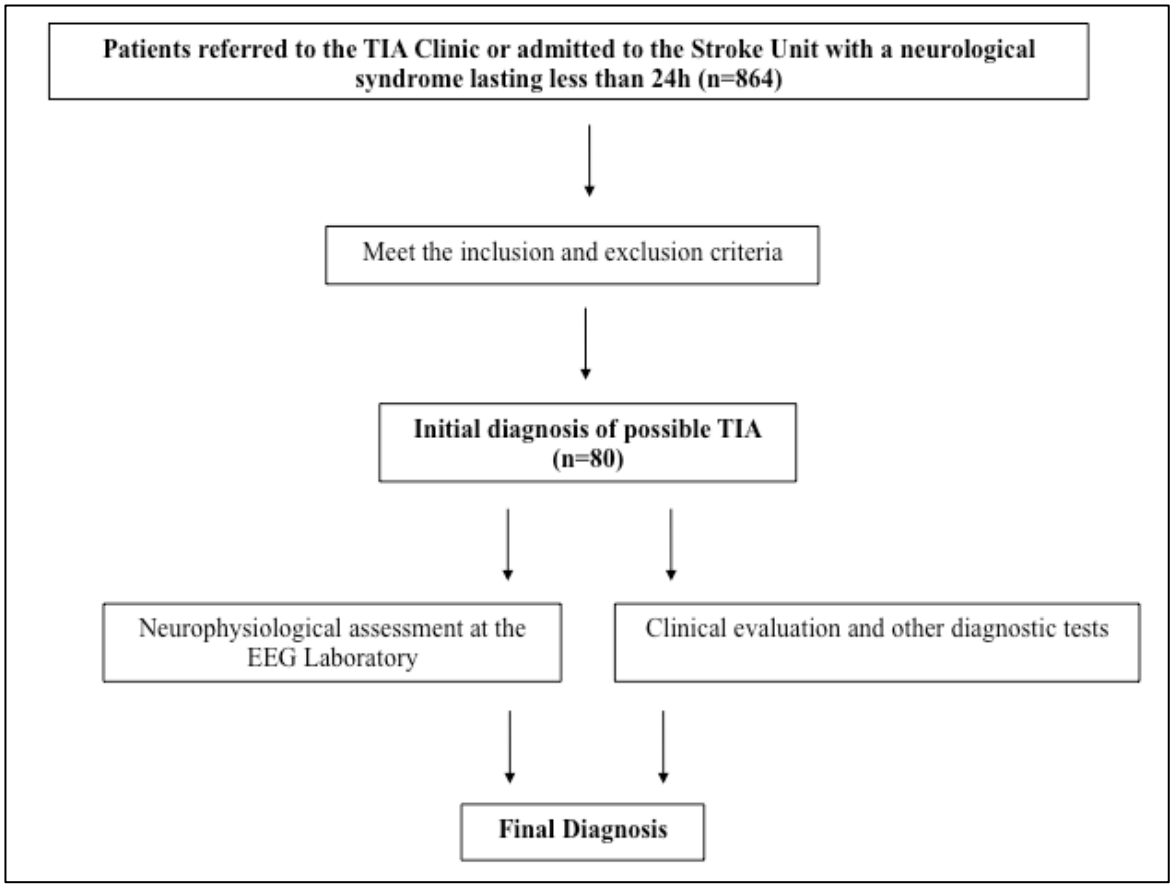
2) What is the percentage of patients with possible TIA with a final diagnosis of epileptic seizure or definitive TIA and which electroencephalographic characteristics differentiate these diagnoses?

2. METHODS

Prospective longitudinal study of patients with a diagnosis of possible TIA evaluated at the TIA Clinic or admitted to the Stroke Unit of the Hospital de Santa Maria (HSM-CHLN), between November 2010 and October 2013. The Ethics Committee "Comissão de Ética para a Saúde" of the HSM-CHLN approved this study.

As inclusion criteria, the patients had to meet the clinical criteria for an initial diagnosis of possible TIA (see definition below) and gave their informed consent. Symptoms suggestive of brainstem/cerebellum involvement were exclusion criteria. The study design is described in **Figure 2**.

Figure 2. Study Design



Legend to figure 2: TIA - Transient Ischaemic Attack

2.1. Standardized clinical and ancillary evaluation[91,92]

Patients were referred to the TIA Clinic by the HSM-CHLN emergency department (ED) or their family doctor. In the ED, patients underwent routine blood tests, ECG and brain non-contrast CT scan (CT) and were prescribed with antiplatelet agents and statins. In the daily TIA Clinic, a stroke neurologist performed a structured clinical interview and physical and neurological examination. On the same day, patients underwent carotid and vertebral duplex scans, transcranial Doppler and blood tests. Transthoracic or transesophageal echocardiography or 24h Holter were ordered, whenever considered necessary. When possible, a MRI including diffusion-weighted imaging (DWI) was done. A neuroradiologist reported all imaging exams. The stroke neurologist, after review of all exams, decided about further treatment, the need for hospitalization and booked the patient for a follow-up appointment one to three months later.

Patients with a possible TIA were admitted to the Stroke Unit, from the ED or TIA Clinic, whenever a definitive diagnosis of TIA was not established, symptoms had not cleared or the patient was judged to be at a high risk of recurrence. The evaluation of admitted patients and their follow-up was similar to those in the TIA Clinic.

The following symptoms associated with possible TIA were systematically recorded: motor, sensory, speech disturbances, partial or total amnesia for the event, consciousness disturbance, and confusional period. Positive symptoms were defined as the occurrence of involuntary movements, sensory symptoms apart from numbness or anaesthesia (such as tingling, stinging, prickling, burning sensations or pain) and visual delusions (palinopsia, polyopia, micro, macro or metaphormopsia), simple (e.g.: lights, spots, oscillating lines with bright, sparkle or colour) or complex hallucinations. The presence of a Jacksonian march of symptoms was considered whenever there was sequential spread of motor (or sensory) symptoms beginning at a specific body region to involve other body parts, accordingly to an electrical disturbance spreading through the homunculus of the motor (or sensory) cortex[199]

Patients were classified in 5 symptomatic groups, not mutually exclusive, taking into account symptom characteristics and their different specificity for the final diagnosis:

1. Motor symptoms
2. Positive phenomena and/or march of symptoms (more frequent in seizures than in TIA)

3. Sensory and/or visual symptoms (posterior brain symptoms)
4. Speech disturbance
5. Amnesia for the event and/or consciousness disturbance and/or confusional period (including consciousness, level or content, disturbance symptoms)

2.2. Diagnostic criteria

The diagnosis of each patient was defined according to the following criteria:

- Initial diagnosis: established at the end of the first observation in TIA Clinic or Stroke Unit by a stroke neurologist (PC).

- Final diagnosis: established after the end of the study by a stroke neurologist (PC), taking into account clinical reassessment 1 to 3 month after the clinical episode, and the result of all diagnostic tests (including early and late EEG). Patients were reclassified in the following final diagnosis groups: TIA; possible TIA; epileptic seizures; other TIA mimic (including migraine; psychiatric disturbance; others). Another neurologist trained in epilepsy (CB), having had access to the same clinical and complementary information, independently reclassified the patients in the same final diagnosis groups.

The following definitions were used for the diagnosis (initial and final):

- Transient ischaemic attack (TIA): Clinical syndrome characterized by sudden focal neurological symptoms, presumed to be of vascular origin, that lasted less than 24 hours[200], regardless of whether or not brain imaging showed a recent ischaemic lesion. This diagnosis group included patients with an acute onset of temporary (less than 24 h) neurological dysfunction consistent with focal brain ischaemia and with supportive or no contradictory complementary diagnostic tests including brain imaging demonstrating or not an acute vascular ischaemic lesion. The typical history for a TIA was a swift onset (no symptoms to maximal symptoms in less than five minutes) of a motor defect, sensory defect, aphasia, loss of vision in one eye or in part of one eye, homonymous hemianopia, or a combination of the above[200]. In these patients an epileptic seizure or another TIA mimic did not cause the clinical syndrome.

- Possible transient ischaemic attack (possible TIA): Neurological syndrome lasting less than 24 hours that do not fulfil international accepted criteria for TIA nor the criteria for a specific mimic diagnosis, although a vascular origin could not be excluded[91,92]. This diagnosis group included patients with odd accompanying symptoms (such as prickles/itching sensations, rigid postures or movement of the limbs), march of symptoms, consciousness disturbance or

amnesia with focal symptoms, multiple stereotyped episodes, positive visual phenomena, isolated speech disturbance/confusion and focal symptoms plus panic or anxiety and paucity of details in the symptoms description[91], without imaging/laboratory evidence of ischaemic cerebral pathology[201] nor of another TIA mimic.

- Transient ischaemic attack mimic (TIA mimic): Focal neurological syndrome lasting less than 24h, for which a non-vascular cause was definitively established according to predefined criteria[91] (e.g.: migraine with aura)[202], metabolic syndrome, transient global amnesia[203,204], panic attack[205], somatoform disorder[205]. An epileptic seizure can also be a TIA mimic but was classified separately in this study.

- Epileptic seizure (seizure): transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain[93]. This diagnosis group included patients with positive motor, sensitive, or sensorial symptoms (as previously described) and also with motionless, unresponsive or automatic behaviour according to stereotyped focal seizures and/or successful response to antiepileptic treatment, epileptiform activity on EEG[206] or the occurrence of an unequivocal seizure in the follow-up. In these patients a TIA and a TIA mimic have been excluded. Accordingly, in patients with possible TIA, the final diagnosis of seizure was established (if other diagnoses were considered excluded after all diagnostic tests and clinical reassessment) in two different circumstances: 1) in patients with possible seizure semiology and epileptiform activity in the EEG; 2) in patients with possible seizure semiology and no epileptiform activity in the EEG but with additional (or better described) clinical events clearly indicative of seizures during the follow-up.

TIA and epileptic seizures were considered the two final diagnoses of interest for this study

2.3. Neurophysiological assessment

All patients underwent a 64-channel video-EEG using a digital Nihon-Kohden device and electrodes placed in accordance with the international 10/10 system and following national and international recommendations[3,207–210] in two different periods: 1) As soon as possible after the possible TIA (early EEG); 2) One month after (late EEG). We intend to repeat EEG, based on guidelines reporting that repeating EEG may be helpful when the diagnosis of epilepsy is unclear[8]. One month after the clinical event was the date chosen for EEG repetition to match the scheduled follow-up clinical visit.

The record had a maximum duration of 60 minutes, including an eye closed wake resting condition and eye open, hyperventilation and photic stimulation manoeuvres.

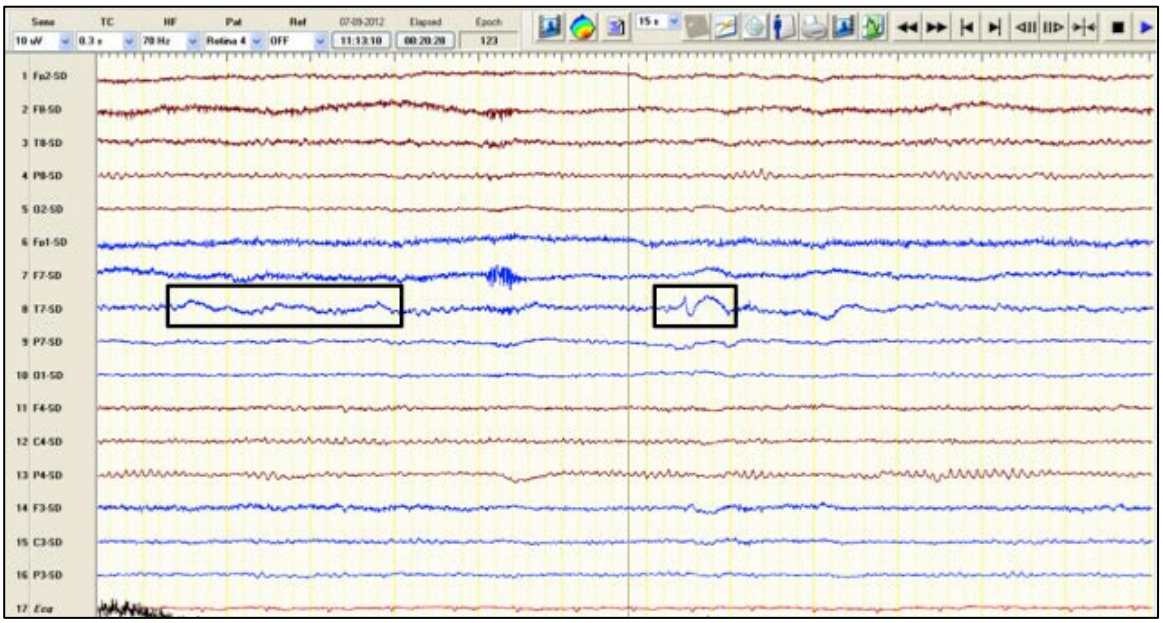
Two clinical neurophysiologists (CB+RP), blinded for the final diagnosis, interpreted the records. Discrepancies were decided by consensus. All EEG records were evaluated for the presence of the following abnormalities: background activity slowing[211]; asymmetry[212]; suppression (focal, hemispheric or diffuse)[212]; focal slow wave activity (including focal and regional concept)[211]; epileptiform activity[211], periodic discharges[212] and others.

The two EEG variables of interest for the present study were Focal Slow Wave Activity (FSWA) and Epileptiform Activity (EA) (**Figure 3**). The following operational definitions were used:

- FSWA: continuous or intermittent slow activity i.e. theta and/or delta band activity[211] limited to an area of the brain or scalp region (includes the concept of focal and regional[211]).
- EA[211]: transients clearly distinguishable from background activity, with a characteristic spiky morphology at a conventional time scale, duration of 70 to 200 ms (sharp wave) or from 20 to under 70 ms (spike) and a main component generally negative relative to other areas

FSWA evolution between early and late EEG was also analysed and considered “persistent” if existing in both exams (even if intermittently), “transient” if present in the early but absent in the late and “absent” if non-existent in both EEG.

Figure 3. Focal Slow Wave Activity and Epileptiform activity



Legend to figure 2: Source derivation montage of a 15mm/sec EEG page. Left black square highlights Focal Slow Wave Activity and right black square identifies Epileptiform Activity (abrupt wave followed by a slow wave).

2.4. Statistics

Univariate descriptive statistics was used for categorical and continuous variables. Bivariate analysis was performed using χ^2 test, Fisher´s exact test or t-student or Mann-Whitney test, as appropriate. The level of significance was established at $\alpha<0.05$ (two-tailed).

To define independent predictors of neurophysiological outcomes, significant variables at $p<0.05$ in the bivariate analysis were tested in multivariate analysis using a stepwise binomial logistic regression with backward elimination. A Hosmer and Lemeshow test assessed the calibration of the model and the Receiver Operator Characteristic (ROC) curve its discriminative capacity.

As a measure of interobserver agreement for the final diagnosis we used Cohen's kappa statistic.

Statistical analysis was performed using SPSS software version 21 for Mac.

3. RESULTS

Eighty patients were included with the initial diagnosis of possible TIA. **Table 3** describes the demographic, clinical, imaging and electroencephalographic characteristics of these patients.

Table 3. Demographic, clinical, imaging and electroencephalographic characteristics of patients with the initial diagnosis of possible TIA

Demographic characteristics		
Male / Female		36 / 44 (45% / 55%)
Age (years)		Mean: 65.5 (SD 14.4); Median: 68.5
Clinical characteristics		
Sudden onset (<1min)		54 (71.1%)
Motor symptoms		20 (25%)
Positive symptoms and/or march of symptoms		40 (50%)
Sensory symptoms and/or visual symptoms		43 (53.8%)
Speech disturbance		43 (53.8%)
Amnesia and/or consciousness disturbance and/or confusional period		36 (45%)
Number of previous episodes		Mean: 2.1 (SD 1.3); Median: 2
Mean duration of the last episode (hours)		Mean: 2.4 (SD 4.8); Median: 0.5
Time between symptoms and EEG (hours)		Mean: 45.8 (SD 37.5); Median: 37.5
Imaging characteristics		
MRI (n=43 / 53.8%)	DWI+	4 (9.3%)
	Another lesion	22 (51.2%)
Electroencephalographic characteristics		
Early EEG (n=80)	FSWA	52 (65%)
	EA	6 (7.5%)
Late EEG (FSWA evolution; n=73 / 91.2%)	Persistent FSWA	43 (58.9%)
	Absent or transient FSWA	30 (41.1%)

Legend to table 3: EA - Epileptiform Activity; FSWA - Focal Slow Wave Activity; DWI+ - acute vascular lesion on Diffusion-Weighted brain magnetic resonance Imaging; SD - Standard Deviation

3.1. Frequency of EEG abnormalities

In the early EEG, 52/80 patients (65%) had FSWA, 6 of them also EA (6/80 7.5%) and 7/80 (11.7%) other abnormalities (increase of beta activity in 5 and diffuse slowing of background activity in 2). The EEG record was reported as normal in 21/80 patients (26.2%).

After one month, 74 patients (92.5%) repeated the EEG, which was normal in 25 (33.8%). In this record, 44/74 (59.5%) patients had FSWA. FSWA evolution was demonstrated persistent in 43 (58.1%), transient in 6 (8.1%) and absent in 24 (32.4%) patients. In one patient (1.4%), FSWA only emerged in the late EEG. Only 3 of the 6 patients with EA in the early EEG retained this activity in the late EEG. No patient showed EA in this exam when not present in the early EEG.

At the time of the early EEG **(Appendix A)**, 11 patients (13.8%) were being treated with antiepileptic drugs (AED). During follow-up, 7 patients (3 with EA in early EEG) were prescribed AED (6 for epileptic seizures and 1 for migraine). At the time of the late EEG, 18 patients (24.3%) were on AED.

3.2. Clinical/Imaging characteristics associated with EEG abnormalities

3.2.1. Age

Both patients with FSWA in the early EEG and patients with demonstrated persistent FSWA in the late EEG were respectively 12.3±3.4 ($t(43.43)=3.63$, $p=0.001$) and 11.3±3.1 years ($t(46.52)=3.66$, $p=0.001$) older than the remaining sample.

There was no significant difference in the mean age of patients with or without EA in the EEG ($t(78)=-1.17$, $p=0.902$).

3.2.2. Neurological syndrome characteristics

No significant associations were found between the variables of the two EEG and the number of previous episodes, duration or the time interval between the clinical event and the EEG.

The electroencephalographic characteristics of the different symptomatic groups under study are depicted in **Table 4**.

Table 4 - Electroencephalographic abnormalities in different symptomatic groups

Type of Symptoms*	Motor		Positive and/or march of symptoms		Sensory and/or Visual		Speech disturbances		Amnesia and/or Impaired consciousness and/or Confusional period	
Early EEG (n=80/100%)	n=20		n=40		n=43		n=43		n=36	
	n	p OR 95% CI	n	p OR 95% CI	N	p OR 95% CI	n	p OR 95% CI	n	p OR 95% CI
FSWA (n=52)	12	0.588 0.750 0.26-2.13	24	0.348 0.64 0.26-1.62	23	**0.020** **0.320** **0.12-0.85**	32	0.057 2,47 0.96-6.34	28	**0.030** **2.92** **1.09-7.81**
EA (n=6)	3	0.162 3.35 0.62-18.16	2	0.675 0.47 0.08-2.75	0	**0.008** **RR=0.42** **0.32-0.55**	5	0.209 4.74 0.53-42.53	4	0.401 2.62 0.45-15.24
Late EEG (FSWA evolution; n=73 / 91.2%)	n=18		n=37		n=39		n=40		n=34	
	n	p OR 95% CI	n	p OR 95% CI	N	p OR 95% CI	n	p OR 95% CI	n	p OR 95% CI
Persistent FSWA (n=43)	10	0.739 0.83 0.28-2.44	20	0.393 0.67 0.26-1.70	16	**0.001** **0.18** **0.06-0.51**	29	**0.009** **3.58** **1.34-9.52**	23	0.156 1.99 0.76-5.16
Absent or transient FSWA (n=30)	8		17		23		11		11	

Legend to table 4: EA - Epileptiform Activity; FSWA - Focal Slow Wave Activity; CI - Confidence Interval; OR - Odds Ratio; RR - Relative Risk

*different symptomatic groups are not mutually exclusive. The bivariate statistical analysis was performed using χ^2 test or Fisher´s exact test having as independent variable each symptomatic group and as dependent variable each EEG characteristic; bold - statistical significance

In the early EEG, FSWA was associated with amnesia for the event and/or consciousness disturbance and/or a confusional period (**Table 4**). In this exam, 5 patients with EA (83%) had a clinical syndrome with speech disturbances and 4 (66.7%) at least one of the following: amnesia for the event, consciousness disturbance and/or confusional period. EA was significant associated with a neurological syndrome with consciousness disturbance (Fisher's exact test, p=0.040, OR=6.59, 95% CI: 1.11-39.15).

In the late EEG, persistent FSWA was associated with the presence of speech disturbances (χ^2=7.41, p=0.006, OR=3.77, 95% CI: 1.42-9.97) and transient FSWA with a confusional period (Fisher's exact test, p=0.047, OR=6.25, 95% CI: 1.04-37.37).

In a binomial logistic regression model, FSWA was no longer predicted (p=0.499, OR=1.47, 95% CI: 1.02-1.11) by "amnesia and/or consciousness disturbance and/or confusional period" when adjusted for age ($\chi^2(2)$ = 14.00, p<0.0005; NagelkerkeR^2=22.1%; Hosmer-Lemeshow test, p=0.839; AUC=0.74, p<0.0005, 95% CI: 0.62-0.87).

Persistent FSWA in the late EEG was independent predicted by both age (p=0.002, OR=1,08, 95% CI: 1.03-1.13) and "speech disturbances" (p=0.02, OR=3.54, 95% CI: 1.22-10.28) in the logistic regression model ($\chi^2(1)$ = 17.73, p<0.0005; NagelkerkeR^2=31.4%; Hosmer-Lemeshow test, p=0.714; AUC 0.80; p<0.0005, 95% CI: 0.69-0.90).

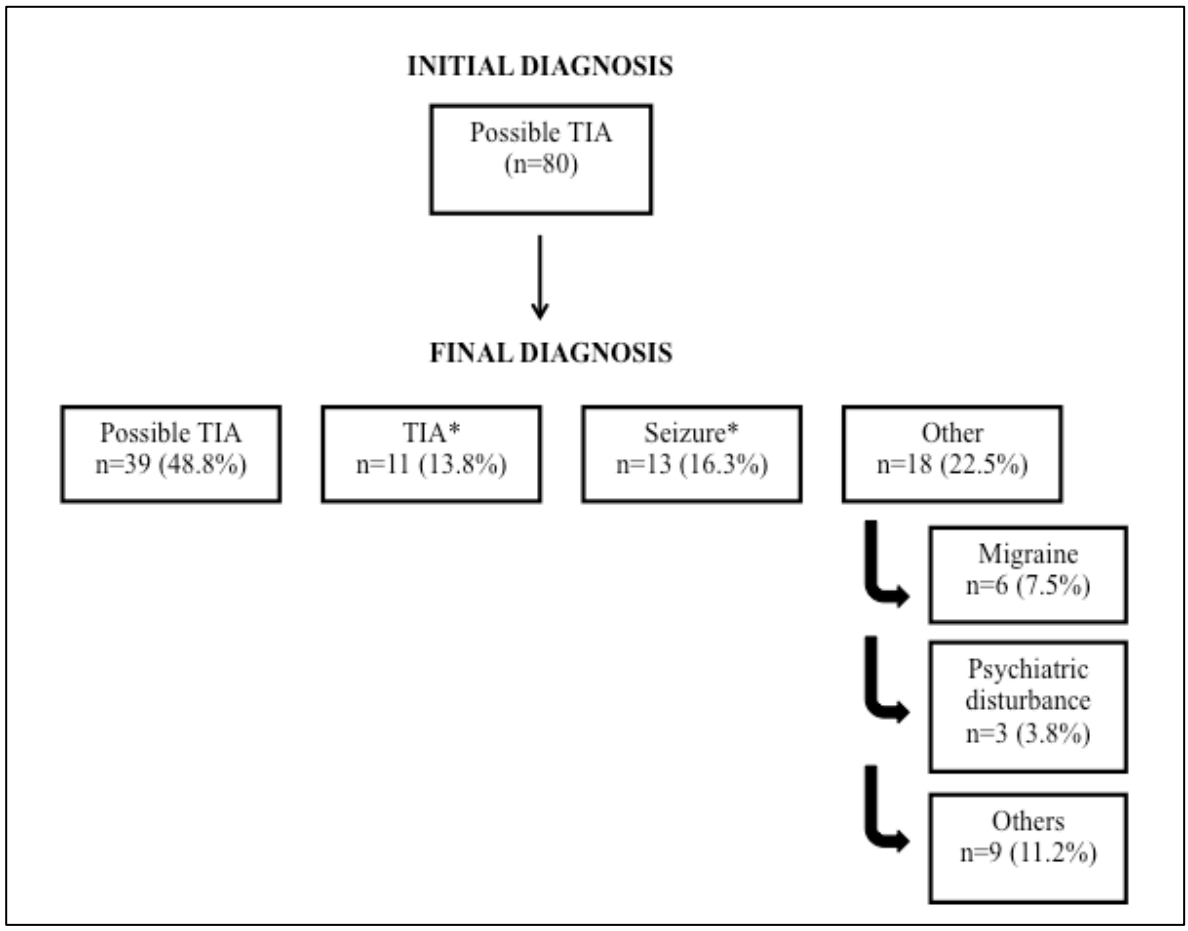
3.2.3. Imaging characteristics

No differences in EEG variables were observed in patients with and without normal MRI. Among patients with an acute vascular lesion in the MRI (DWI+), three (75%) had FSWA in the early EEG and in two of them (66.7%) this activity disappeared in the late EEG (Fisher's exact test, p=0.011).

3.3. Final diagnosis of epileptic seizure or definitive TIA in patients with possible TIA

After all diagnostic tests and clinical reassessment, patients with possible TIA were reclassified in a final diagnosis (**Figure 4**).

Figure 4. Reclassification of possible TIA



Legend to figure 4: *one patient classified as TIA had the concomitant diagnosis of epileptic seizures (partial complex seizures) in the clinical follow-up

Thirteen patients were diagnosed with epileptic seizures (16.3%) and 11 (13.8%) with definitive TIA by the stroke neurologist (PC). One patient had a final dual diagnosis of definitive TIA and epileptic seizures. This patient was discharged from the Stroke Unit with a TIA diagnosis. However, in the follow-up appointment the patient reported different clinical episodes that were then diagnosed as partial complex seizures.

3.3.1. Interobserver agreement

The two neurologists agreed in the diagnosis of 59 patients (73.8%). The interobserver concordance in the final diagnosis was good (k=0.627, p<0.0005, 95% CI: 0.48-0.77). In the analysis of the diagnosis of seizure (vs. non-seizure), the two classifiers agreed in 73 patients (91.2%). The interobserver agreement was good (k=0.707, p<0.0005, 95% CI: 0.50-0.91). Also, for the diagnosis of definitive TIA (vs. non-definitive TIA) the interobserver agreement was good (k=0.789, p<0.0005, 95% CI: 0.59-0.99), with a concordant diagnosis in 76 patients (95%).

3.3.2. Clinical/Imaging characteristics associated with the final diagnosis of interest

No significantly mean age difference was found between patients with final diagnosis of epileptic seizures or TIA and other final diagnosis (t(65.85)=1.474, p=0.145).

Clinical and EEG characteristics of patients with the final diagnosis of seizures and definitive TIA are displayed in **Table 5.**

Of the evaluated symptoms, only the existence of a Jacksonian march of symptoms was more frequent in seizure patients (n=7; 50%) than in patients with definitive TIA (n=1; 9.1%) (Fisher's exact test, p=0.027, OR=14.00, 95% CI: 1.33-147.43).

MRI was performed on eight (66.7%) patients with epileptic seizures and five (45.4%) patients with the final diagnosis of definitive TIA, four of whom (80%) had an acute vascular lesion in MRI.

Table 5. Clinical characteristics of the patients with a final diagnosis of seizures and TIA

	Final Diagnosis		
	Seizures* (n=12)	TIA* (n=11)	p
Age in years (SD)	68.2 (10.4)	68.9 (9.1)	0.874
Total duration of symptoms in hours (SD)	1.3 (1.5)	1.8 (2.6)	0.695
Number of previous episodes (SD)	2.8 (1.8)	2.4 (1.6)	0.874
Time between symptoms and EEG in hours (SD)	34.6 (32.3)	38.2 (26.1)	0.561
Symptoms			p OR, 95%CI
Motor symptoms	4 (33.3%)	6 (54.5%)	0.414 0.417, 0.08-2.25
Positive symptoms and/or march of symptoms	7 (58.3%)	3 (27.3%)	0.214 3.73, 0.65-21.58
Sensory and/or visual symptoms	3 (25%)	5 (45.4%)	0.400 0.40, 0.07-2.34

		Seizures* (n=12)	TIA* (n=11)	p OR, 95%CI
Symptoms				p OR, 95%CI
Speech disturbances		8 (66.7%)	8 (72.7%)	1.000 0.75, 0.12-4.49
Amnesia and/or Consciousness disturbance and/or Confusional period		7 (58.3%)	5 (45.4%)	0.537 1.68, 0.32-8.76
Electroencephalographic characteristics				p OR, 95%CI
Early EEG	FSWA	11 (91.7%)	8 (72.7%)	0.317 4.12, 0.36-47.30
	EA	5 (41.7%)	1 (9.1%)	0.155 7.14, 0.68-75.22
Late EEG (FSWA evolution)	Persistent FSWA	11 (91.7%)	5 (45.4%)	**0.027** **13.20, 1.24-140.68**
	Absent or transient FSWA	1 (8.3%)	6 (54.5%)	

Legend to table 5: EA - Epileptiform Activity; FSWA - Focal Slow Wave Activity; TIA – Transient Ischaemic Attack; *The patient who had the final dual diagnosis of TIA and seizures is included in this table only in the TIA group because the clinical episode that provoked the admission to the Stroke Unit had the final diagnosis of TIA

3.4. Electroencephalographic characteristics in patients with epileptic seizure and definitive TIA diagnosis

FSWA in the early EEG was differently distributed between final diagnosis groups (p=0.027). Furthermore, FSWA in the early EEG was associated with the final diagnosis of epileptic seizure or definitive TIA compared to other type of final diagnosis (19/23 patients versus 33/57 patients; p=0.041; OR 3.46; 95% CI 1.04-11.46).

The only significant EEG difference between patients with epileptic seizures and definitive TIA was a different evolution of FSWA between the early and the late EEG (**table 5**). The chance of persistent FSWA in the late EEG was significantly greater (13.2 times higher) in a patient with an epileptic seizure than in a patient with TIA. In fact, the majority of patients with seizures (91.7%) maintained the FSWA between the two examinations while the same only occurred in less than half (45.5%) of TIA patients. Furthermore, absent or transient FSWA was less frequent in patients with seizures (8.3%) than with TIA (54.5%).

Although a higher percentage of patients with epileptic seizures had EA, this difference was not statistically significant. Of the 13 patients who had the final diagnosis of epileptic seizures, six (46.2%) had EA in the early EEG.

4. DISCUSSION

FSWA was the commonest EEG abnormality found in the early EEG of patients with possible TIA but did not distinguished between TIA and seizure patients. In patients with seizures, FSWA was more common than epileptiform activity and its presence in the EEG one month later was more likely in patients with epileptic seizures.

In this work, EEG abnormalities were frequent, occurring in 73.8% of the patients. FSWA was the most common, although others could be identified. This percentage is similar to that found by De Reuck & Van Maele[50] in patients with inhibitory seizures (76%), but rather different from that of patients with definitive TIA (7.6%) in the same study. Unlike this Belgian study, we did not recognise early EEG differences between epileptic seizure and definitive TIA patients. There are some plausible explanations for this apparent discrepancy between the two studies, namely time until EEG and age. Neurological syndromes lasting less than 24 hours are, by definition, time-limited events of neurological dysfunction and, for that reason, time interval between clinical manifestations and EEG might influence the presence or the type of electroencephalographic abnormalities. In the De Reuck and Van Maele study, 100% of patients with seizures but less than half of patients with definitive TIA underwent an EEG in the first 24 hours. Furthermore, temporal slowing is a frequent finding in older patients[213] and seizure patients were older than TIA patients in the same study. In our series, time until EEG and age were not significantly different in patients with seizures and with TIA.

In this series of possible TIA patients, epileptic seizures were the most common final diagnosis, followed by definitive TIA. Approximately one half of the patients remained undiagnosed, clearly showing the differential diagnosis difficulty of possible TIA and the need for complementary strategies supporting the classification of these undefined events[17]. Sequential spread of symptoms according to the homunculus of the motor (or sensory) cortex were associated with the diagnosis of epileptic seizures, in agreement with the "Jacksonian march" characteristic of focal seizures[214].

In our work, patients with early FSWA had a higher probability of subsequent diagnosis of epileptic seizures or definitive TIA, not explained by a different mean age between final

diagnosis groups. Furthermore, a higher percentage of patients with these final diagnoses had early FSWA compared to early EA (82.6% vs. 26.1%, respectively). Although FSWA is not specific to the final diagnosis, it was informative and more sensitive than EA. In line with these results, a patient with a possible TIA with early FSWA should be further investigated and followed-up.

Six patients (7.5%) had EA in the early EEG, a higher percentage than the reported frequency of false-positive (0.5-1%) in asymptomatic individuals[215,216]. The percentage of patients with a definite diagnosis of epileptic seizures and EA in the early EEG (46.2%) is within the range of sensitivity reported for EEG (26 to 56%) as a diagnosis test for epilepsy[8]. Still, it is possible that AED prescription in 14% of the patients reduced the probability of finding EA in the early EEG[217–220]. Furthermore, focal seizures arising from small foci or deep foci for the recording electrodes may not have a surface EEG correlate. It is known that the repetition of EEG can be useful when the diagnosis of epilepsy is not clear[8,221]. Salinsky and collaborators[222] showed that 50% of epilepsy patients had EA in the first EEG, 84% in the third EEG and 92% in the fourth EEG. However, in our study, the repetition of the EEG did not improve the EEG value in EA detection, as would be expected. There are two possible reasons for this finding. On the one hand, there is the already discussed effect of AED in the intercritical EA[217–220]. In fact, the percentage of medicated epileptic seizures patients by the time of late EEG was greater than in early EEG (92.3%. vs. 38.5%). On the other hand, the likelihood of finding EA in the EEG seems to decrease over time after a paroxysmal event[223]. The lack of a significant difference in the incidence of EA in the EEG of patients with the final diagnosis of seizure and TIA is likely to be due to small patient numbers in each subgroup.

The time evolution pattern of FSWA was significantly different between the two final diagnostic groups (seizures and TIA), as patients with seizures more often had FSWA persisting in the late EEG. The high percentage of epileptic seizure patients with early FSWA and the persistence of FSWA in the late EEG in these patients, may represent a neurophysiologic marker of the existence of an enduring predisposition to generate epileptic seizures[93,146]. In fact, FSWA has been described in patients with epilepsy as a good marker of the epileptogenic network and the ictal onset zone[224–227]. In contrast, patients with definitive TIA had a different FSWA time evolution pattern: either they never had FSWA in

the early EEG or the FSWA was no longer present in the late EEG, in accordance with what was described in transitory cerebral ischaemia due to carotid compression[228].

This work has some strengths, such as: 1) it compares EEG differences between patients who initially had transient neurological symptoms and a not yet established neurological diagnosis, reflecting the clinical practice diagnostic question - is the EEG useful when the diagnosis is unknown?; 2) EEG readers were blind to the final diagnosis, which was established only after the EEG report; 3) no patients were lost for clinical follow-up and only a few (7.7%) for the EEG follow-up; and 4) the high final diagnosis interobserver agreement gives robustness to the results. Nevertheless, this study also has some limitations, in particular: 1) it was hospital-based limiting generalization to other clinical settings; 2) A time-based TIA definition was used, so these results may not apply to tissue-based defined TIA[127,229]; 3) Only two EEG abnormalities were variables of interest in this study but others could be considered; 4) the sample size was modest, which limits the statistical power for some comparisons.

5. CONCLUSIONS

In the early EEG, the majority (58.3%) of patients with a final diagnosis of an epileptic seizure did not have EA. FSWA in the early EEG occurred whether the patient suffered a seizure or TIA (and was more often present than EA following a seizure), but in the EEG performed 1 month after the clinical episode was more likely to indicate that the initial event was a seizure.

V. PROJECT 2

"The statistical analysis of a large collection of results from individual studies for the purpose of integrating the findings"

Gene Glass

FREQUENCY OF POST-STROKE EPILEPTIFORM ACTIVITY - A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES

AUTHORS

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ABSTRACT

Introduction: Cerebrovascular diseases are the most frequent risk factor for epilepsy in the elderly, and epileptic phenomenon following stroke is known to worsen the prognosis. Although electroencephalography is the gold standard epilepsy biomarker, it is rarely used in post-stroke studies, and the frequency of post-stroke epileptiform activity is still uncertain.

Patients and methods: We analysed studies indexed to MEDLINE, Embase, Web of Science, PsycINFO and OpenGrey (up to March 2015), reporting post-stroke electroencephalographic epileptiform activity frequency in adults. Epileptiform activity was classified as ictal (electrographic seizures) and interictal (non-periodic spikes and sharp waves). Data selection, extraction and appraisal were done in duplicate. Random-effects meta-analysis was used to pool frequencies.

Results: The pooled frequency of post-stroke ictal and interictal epileptiform activity was 7% (95%CI 3%-12%) and 8% (95%CI 4%-13%), respectively. The use of continuous electroencephalogram was not associated with an increased frequency of electrographic seizures (p=0.05), nor did the management setting (Intensive Care Unit [ICU] versus non-ICU, p=0.31). However, studies with continuous electroencephalogram showed a higher frequency of interictal epileptiform activity (p=0.01).

Discussion: This study provides the best available estimates of the frequency of post-stroke electroencephalographic epileptiform activity. Due to detection bias, it was not possible to correlate clinical and electrographic seizures.

Conclusion: The frequency of ictal and interictal epileptiform activity in the EEG was comparable with previous frequency analyses of clinical seizures. The frequency of ictal epileptiform activity did not change with continuous record or clinical setting, while the frequency of interictal epileptiform activity increased with continuous record.

KEY-WORDS
epileptic seizures, stroke, EEG, systematic review, meta-analysis

1. INTRODUCTION

Cerebrovascular diseases are the most frequent risk factor for epilepsy[19], accounting for more than half of all cases in elderly patients[20]. On the other hand, epileptic seizures following stroke[44,45] and electrographic seizures and interictal epileptiform discharges in critically ill patients[46–48] are known to worsen the outcome.

The current International League Against Epilepsy (ILAE) definition of epilepsy[93] allows for the diagnosis of epilepsy after a single unprovoked seizure, provided that there is at least a 60% probability of recurrence, as it is the case of the first unprovoked seizure after the acute stroke phase[44]. This sensitivity-maximizing definition, and the fact that acute symptomatic seizures are described as risk factors for unprovoked seizures[230], prompts discussion for the role of electroencephalogram (EEG) after stroke – as this technique can contribute to early and accurate detection of ictal and interictal epileptiform activity.

The frequency of seizures and interictal epileptiform activity after stroke is uncertain[27]. This is the case because EEG is seldom used in studies investigating the frequency of post-stroke seizures, although being the gold standard for the identification of these phenomena[5], and as little as 10% of all seizures are recognised without EEG in critically ill patients[75].

As so, we set out to estimate the frequency of post-stroke electroencephalographic epileptiform activity using meta-analytical techniques.

2. METHODS

2.1. Protocol and registration

The protocol followed the PRISMA-P guidelines and was registered at **Prospero (CRD42015029362)**[231]. We followed the MOOSE and PRISMA guidelines[232]. Statistical data reporting followed the SAMPL guidelines.

2.2. Eligibility criteria

We included published and unpublished (i.e. conference proceedings) observational studies reporting original data on the frequency of electroencephalographic epileptiform activity after stroke in adults (≥18-year-old). All observational study designs were accepted with the exception of case series with less than 10 participants to decrease the risk of selection bias. This threshold was established arbitrarily and excludes single case-reports and small case-series. Studies reporting on patients diagnosed with silent cerebral infarcts and haemorrhages were excluded due to the low specificity to determine a time sequence between the cause and the effect. No study was dismissed a priori due to poor quality, language, or length of follow-up. Epileptiform activity in the EEG was classified as ictal activity (electrographic seizures[212]) and interictal activity (non-periodic spikes and sharp waves[211]). Stroke was defined as an episode of acute neurological dysfunction presumed to be caused by ischaemia or haemorrhage, persisting ≥24 hours or until death[233]. For data extraction and analysis, we followed the above-mentioned definitions.

2.3. Information sources

The electronic search was conducted in MEDLINE, Embase, Web of Science, and PsycINFO. Grey literature was searched via OpenGrey. No language, date/time, document type or publication type restriction was applied. The last search was done on 22 March 2015. Search results were de-duplicated in EndNote X7. Non-English reports were translated. Whenever needed, authors were contacted for further data. The reference lists of included studies were crosschecked for additional studies.

2.4. Search

The search strategies developed combine the terms (Cerebrovascular disorder OR Stroke OR Brain Ischaemia OR Brain Infarction OR Intracranial Embolism and Thrombosis OR Intracranial Haemorrhage OR Cerebral Haemorrhage OR Subarachnoid Haemorrhage OR

Cerebral Infarction OR Cerebellar Infarction OR Cerebellar Haemorrhage OR Brain Stem Infarction OR Brain Stem Haemorrhage) with (Partial Epilepsy OR Generalized Epilepsy OR Post-Traumatic Epilepsy OR Reflex Epilepsy OR Seizure OR Status Epilepticus). A filter was adapted to avoid retrieval of non-observational studies. The search strategy was restricted to humans as participants. All terms were searched as free-text and controlled vocabulary. The search strategies can be found in the **Appendix B**

2.5. Study selection

Reports retrieved through electronic identification were screened by title and abstract. The full-text of potentially eligible studies was screened for appropriateness for inclusion. Three independent screeners (CB, DS, and RP) conducted this process. Disagreements were solved by consensus, or by a forth party (FBR).

2.6. Data collection process

A pilot extraction form was tested with 5 studies by two independent reviewers (CB and FBR). Two independent parties (AF, DS, GSD, HN, RM, or ARP) extracted data from included studies to a predetermined and piloted electronic form using the online-based software Covidence (https://www.covidence.org/). Disagreements were solved by an independent party (CB or FBR).

2.7. Risk of bias in individual studies

The risk of bias of individual studies was evaluated in accordance with the Newcastle-Ottawa Quality Assessment Scale[234]. Quality of reporting was independently analysed by two authors (AF, DS, GSD, HN, RM, or ARP). Disagreements were solved by a third party (CB or FBR). Studies having a star rating of more than 60% were considered of low risk of bias, as assumed by others.

2.8. Summary measures

The primary outcomes were the frequency of ictal and interictal epileptiform activity (as defined above) in stroke patients' EEGs. To calculate frequencies, we adopted a conservative approach by determining the number of events divided by the number of participants in the study. This method underestimates events, since not all participants performed EEG.

2.9. Synthesis of results

We used Stata/SE 14.0 software to conduct the analysis and to derive forest plots. Random-effects meta-analysis weighted by the inverse-variance method was performed to estimate the pooled frequencies and respective 95% confidence intervals (95% CI). We used a random-effects model as substantial heterogeneity between studies results was expected. Heterogeneity was assessed with the I^2 test. The limit for statistical significance was established at 0.05.

2.10. Additional analysis

Pre-specified sensitivity analyses were conducted by excluding: studies at high and unclear risk of bias; studies without continuous EEG (cEEG); and studies in settings other than the intensive care unit (ICU). We planned to estimate the frequency of events in different subgroups of patients according to study site, year, stroke type and location. Unfortunately, we could not retrieve enough data for the latter analysis. Two post-hoc analyses were performed: the first excluding studies only reporting on subarachnoid haemorrhage (SAH), to study the effect of this aetiology on the overall frequency of events; and the second solely including studies where EEG was performed in a consecutive cohort of stroke patients, to study the effect of selection bias.

3. RESULTS

3.1. Study selection: The last electronic search was run from inception to March 22, 2015. A total of 2871 references were retrieved (MEDLINE 1985, Embase 425, PsycINFO 66, Web of Science 394, Open Grey 1). Two studies were included via hand-search. After de-duplication, 2527 titles and abstracts were screened, and 2226 were excluded, as they were not relevant to our research question. We selected 301 studies for full text assessment, and 284 studies were removed due to failure to comply with inclusion criteria. A total of 17 studies where included (**Figure 5**, **Table 6** and **Appendix C**).

Figure 5. PRISMA flow chart

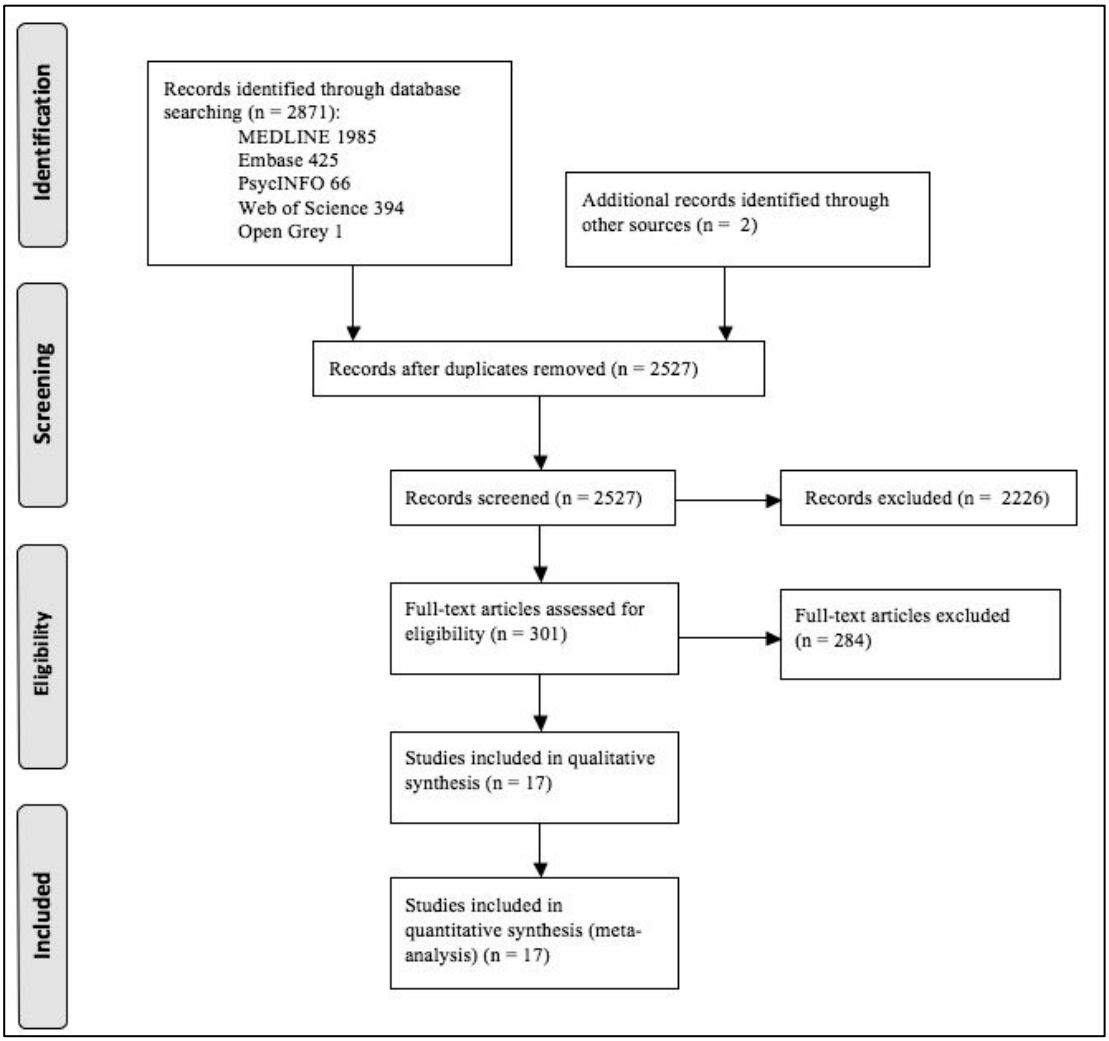


Table 6. Characteristics of included studies

Study	Year	Country	n	EEG type	Stroke type	Setting
Arboix 1997	1997	Spain	1220	EEG	Ischaemic and haemorrhagic	Neurology department
Dhanuka 2001	2001	India	269	EEG	Ischaemic and haemorrhagic	Neurology department
Velioglu 2001	2001	Turkey	1174	EEG	Ischaemic and haemorrhagic	Neurology department
Vespa 2003	2003	USA	109	cEEG	Ischaemic and haemorrhagic	Intensive care unit
Claassen 2004	2004	USA	209	cEEG	Ischaemic and haemorrhagic	Tertiary care hospital
Carrera 2006	2006	Switzerland	100	cEEG	Ischaemic and haemorrhagic	Stroke unit
Claassen 2006	2006	USA	116	cEEG	Haemorrhagic	Intensive care unit
Claassen 2007	2007	USA	102	cEEG	Haemorrhagic	Tertiary care hospital
Little 2007	2007	Italy	889	cEEG	Haemorrhagic	Tertiary care hospital
Naidech 2009	2009	USA	98	cEEG	Haemorrhagic	Tertiary care hospital
Garrett 2009	2009	USA	110	cEEG	Haemorrhagic	Tertiary care hospital
Strzelczyk 2010	2010	Germany	264	EEG	Ischaemic and haemorrhagic	Neurology department
Chen 2011	2011	China	32	EEG	Ischaemic and haemorrhagic	Geriatric department
Lindgren 2012	2012	Sweden	108	cEEG	Haemorrhagic	Intensive care unit
Srinivasan 2013	2013	USA	138	EEG	Haemorrhagic	Tertiary care hospital
O'Connor 2014	2014	USA	69	cEEG	Haemorrhagic	Intensive care unit
Swisher 2015	2015	USA	56	cEEG	Ischaemic and haemorrhagic	Intensive care unit

Legend to table 6: EEG - spot EEG; cEEG - continuous EEG; n - number of patient enrolled per study

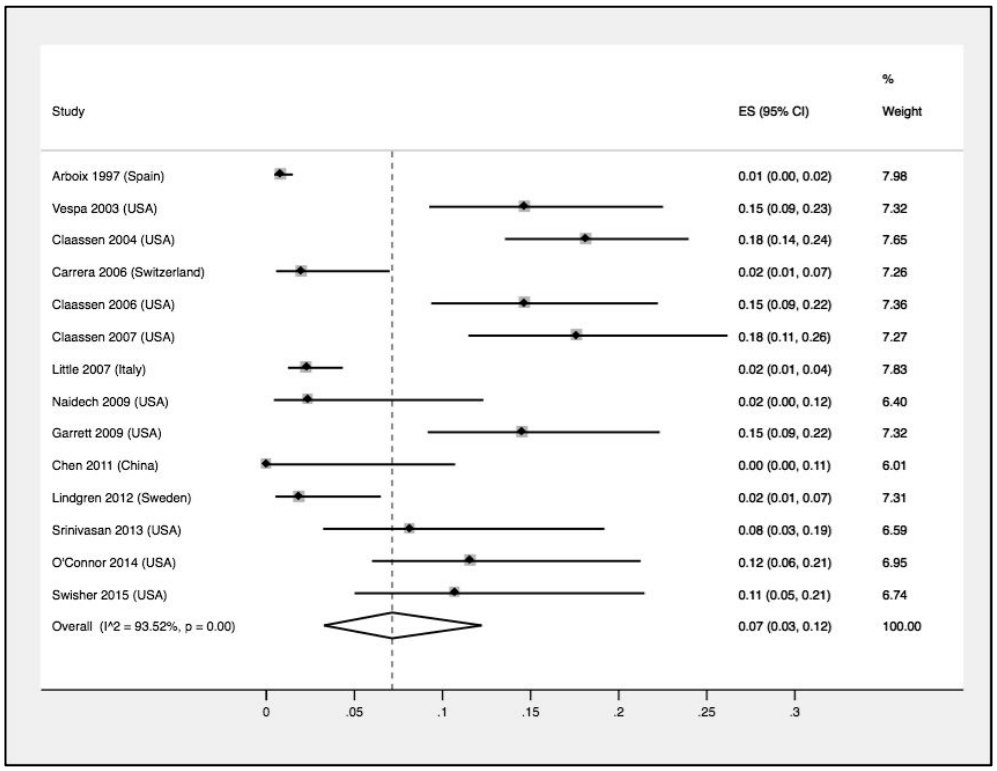
3.2. Risk of bias within studies: Four (23.5%) studies did not meet our definition of low risk of bias. The remaining were assessed as being at a low risk of bias. Only 2 (11.7%) included studies attained the maximum quality score (low risk of bias in all domains).

3.3. Synthesis of results

3.3.1. The pooled frequency of ictal epileptiform activity (electrographic seizures)

The pooled frequency of ictal epileptiform activity (electrographic seizures) in the EEG was 7% (95% CI 3% to 12%, I^2= 93.5%, 14 studies, n=2711, **Figure 6**), without significant differences when considering only studies at low risk of bias (13 studies), studies exclusively enrolling participants with haemorrhagic stroke (8 studies), studies including ischaemic and haemorrhagic stroke (6 studies), or after excluding studies where only SAH were captured (13 studies). Studies where EEG was performed in a consecutive cohort of stroke patients showed a smaller frequency of events (4%, 95% CI 0% to 12%, I^2=82.5%, 4 studies, n=339). No study exclusively enrolled participants with ischaemic stroke. Studies including exclusively SAH patient did not differ from the other included studies (p=0.77). The use of cEEG was not associated with an increased frequency of detected electrographic seizures (p=0.05), nor with the setting where the patients were tested (ICU versus non-ICU, p=0.31), or the year of publication (before versus after 2007, a threshold generated by splitting the included studies into two groups according to the year of publication) (p=0.72). Studies performed in the USA showed a higher frequency of electrographic seizures than studies performed outside the USA (13% (95% CI 10% to 17%) versus 1% (95% CI 0% to 2%); p<0.001)

Figure 6. Pooled frequency of ictal activity (electrographic seizures)

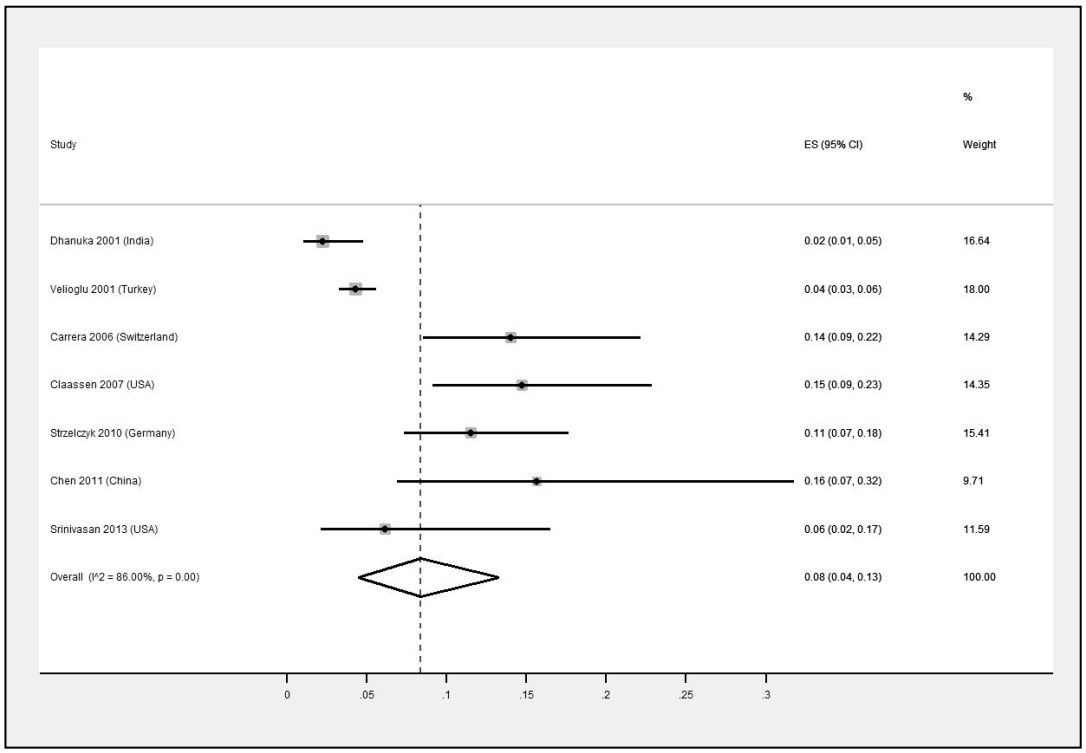


Legend to figure 6: This graph shows the results of each individual study in each of the lines, and the results of the meta-analysis in the last line (lozenge). The left column presents the surname of the first author of each study, the year of publication, and the country where the study was performed, with the exception of the last line, where the results of the statistical heterogeneity tests employed are presented. The two middle columns show, from the left to the right, the graphical (forest plot) and numerical representation (percentage of participants with ictal activity and a 95% confidence interval [95% CI]) of the results of each individual study and, on the last line (lozenge), of the meta-analysis. The dotted vertical line represents the central estimate of effect. Finally, the right column depicts the weight each of the studies had on the meta-analysis.

3.3.2. The pooled frequency of interictal epileptiform activity

The pooled frequency of interictal epileptiform activity (non-periodic spikes and sharp waves) was 8% (95% CI 4% to 13%, I^2=86.0%, 7 studies, n=1874, **Figure 7**). When only analysing trials at low risk of bias, the estimated frequency increased to 10% (95% CI 5% to 16%, I^2=85.48%, 6 studies, n=1810). We found no difference for studies including ischaemic and haemorrhagic stroke (8%, 95% CI 3% to 13%, I^2=87.2%, 5 studies, n=1839), though we found an increased frequency among studies exclusively enrolling haemorrhagic stroke patients (12%, 95% CI 7% to 13%, I^2=96.8%, 2 studies, n=240). No study reported solely on patients with SAH. Studies where EEG was performed in a consecutive cohort of stroke patients showed a higher frequency of events (14%, 95% CI 9% to 21%, I^2=0.0%, 2 studies, n=132). Studies with cEEG showed a higher frequency of interictal epileptiform activity detection (14%, 95% CI 10% to 20% vs. 6%, 95% CI 3% to 10%; p=0.01). No study performed in ICU reported these events and no differences were found between study site (p=0.26) or year of publication (p=0.29).

Figure 7. Pooled frequency of interictal activity (non-periodic spikes and sharp waves)



Legend to figure 7: This graph shows the results of each individual study in each of the lines, and the results of the meta-analysis in the last line (lozenge). The left column presents the surname of the first author of each study, the year of publication, and the country where the study was performed, with the exception of the last line, where the results of the statistical heterogeneity tests employed are presented. The two middle columns show, from the left to the right, the graphical (forest plot) and numerical representation (percentage of participants with interictal activity and a 95% confidence interval [95% CI]) of the results of each individual study and, on the last line (lozenge), of the meta-analysis. The dotted vertical line represents the central estimate of effect. Finally, the right column depicts the weight each of the studies had on the meta-analysis.

4. DISCUSSION

This systematic review and meta-analysis of observational studies shows that 7% and 8% of patients following a stroke have epileptiform ictal and interictal activity, respectively, in the EEG. To the best of our knowledge, the frequency of post-stroke electroencephalographic events in observational studies was never pooled, and such results should prompt further discussion as to whether EEG should be used more frequently after stroke as a biomarker for epileptic manifestations.

Previous systematic reviews have shown that intracerebral haemorrhages and SAH are associated with a significantly greater probability of epileptic seizures[26,235]. In our study, studies exclusively enrolling haemorrhagic stroke patients showed a higher frequency of interictal epileptiform activity but not of electrographic seizures. Furthermore, the frequency of events was not different in studies solely focused on SAH. Importantly, the absence of studies exclusively enrolling ischaemic stroke patients may bias these results, since mixed population studies (i.e. including both ischaemic and haemorrhagic stroke) are expected to set the bar for this comparison much higher and decrease the likelihood of finding a statistically significant difference between populations. Also, the low number of studies analysing epileptiform activity in haemorrhagic stroke in general, and in SAH in specific, can also contribute to uncertainty and to unexpected results, as there is a pathophysiological rational for these stroke subtypes to be associated with more epileptiform activity.

As expected, in studies where consecutive stroke patients underwent an EEG, the frequency of ictal events was lower than our general estimate. This analysis subtracts from the selection bias introduced by retrospective studies where it is methodologically difficult to avoid a systematic error of including participants more likely to have epileptiform activity, such as those with clinical seizures or with a lower or fluctuating consciousness level. Unfortunately, our confidence in these results is low due to limited statistical power and low precision. Unexpectedly, the frequency of interictal events in these studies exceeds the general estimate, though the reason for this finding may be the lack of power, since only 2 studies were included.

In our study, cEEG did not increase the likelihood of detection of ictal epileptiform activity, which agrees with previous studies[76], where it was stated that insufficient data exists to

support the benefit of cEEG over spot EEG recordings. That being said, the detection rate of interictal epileptiform activity with cEEG was twice as high without cEEG.

The frequency of electrographic seizures was not different in ICU and non-ICU patients. However, the scarcity of studies and the imbalances between population characteristics may bias these results.

Not unexpectedly, the year of publication did not influenced the frequency of events. On the other hand, it was interesting to note that studies conducted in the USA showed a statistically significant higher frequency of ictal events. We hypothesise that this can be explained by the population characteristics, since a great majority of the North American studies were based in an intensive care setting, while this was not true for the other studies.

Finally, it is important to note that this study has several limitations. The quality assessment showed that almost 80% of the studies were at low risk of bias but only 12% had a high-quality standard. Our methodological options probably underestimate electroencephalographic epileptiform activity. EEG is more likely to be requested if there is a clinical suspicion of seizures. This selection bias by indication is only avoidable in prospective studies where EEG is performed on all patients regardless of the clinical features. Studies reporting electroencephalographic epileptiform activity are not controlled with a group of participants without the pathological condition of interest, but who were subject to the same kind of clinical and diagnostic procedures. This invalidates the possibility of studying risks of events instead of frequency as we did. It would be interesting to understand how the frequency of clinical seizures relates to the frequency of electrographic ones. Unfortunately, due to diagnostic bias, since not all enrolled participants performed EEG, the available literature cannot reliably answer this question. Finally, we would like to have included the timing of the EEG in our analyses, since this variable seems to be closely related with the likelihood of detection of epileptiform events. Unfortunately, this data was rarely available.

5. CONCLUSION

In conclusion, the frequency of ictal and interictal epileptiform activity in the EEG was comparable with previous frequency analyses of clinical seizures. The frequency of ictal epileptiform activity did not change with continuous record or clinical setting, while the frequency of interictal epileptiform activity increased with continuous recordings

VI. PROJECT 3

"It is not very uncommon to find when a patient has recovered or is recovering from hemiplegia, the result of embolism of the middle cerebral artery or of some branch of this vessel, that he is attacked by convulsion beginning in some part of the paralyzed region"

John Hughlings Jackson (1864)

POST-STROKE SEIZURES ARE CLINICALLY UNDERESTIMATED

AUTHORS

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ABSTRACT

Introduction: Cerebrovascular disease is the leading cause of epilepsy in adults, although post-stroke seizures reported frequency is variable and few studies used EEG in their identification.

Objectives: To describe and compare EEG and clinical epileptic manifestations frequency in patients with an anterior circulation ischaemic stroke.

Method: Prospective study of acute anterior circulation ischaemic stroke patients, consecutively admitted to a Stroke Unit over 24 months and followed-up for one year. All patients underwent standardized clinical and diagnostic assessment. Seizure occurrence was clinically evaluated during hospitalization and by a telephone interview at 6 months and a clinical appointment at 12 months after stroke. Video-EEG was performed in the first 72 hours (1st EEG), daily after the 1st EEG for the first 7 days after the stroke, or later if neurological worsening, at discharge, and at 12 months.

Results: 151 patients were included (112 men) with a mean age of 67.4 (11.9) years. In the 1st year after stroke, 38 patients (25.2%) had an epileptic seizure.

During hospitalization, 27 patients (17.9%) had epileptiform activity (interictal or ictal) in the EEG, seven (25.9%) of them electrographic seizures. During the first week after stroke, 22 (14.6%) patients had a seizure and 4 (2.6%) non-convulsive *status epilepticus* criteria. Five (22.7%) acute symptomatic seizures were exclusively electrographic.

At least one unprovoked seizure occurred in 23 (15.2%) patients.

Conclusion: In the first 7 days after stroke, more than one-fifth of patients with seizures had exclusively electrographic seizures. Without a systematic neurophysiological evaluation the frequency of post-stroke seizures are clinically underestimated.

KEY-WORDS

ischaemic stroke, symptomatic seizures, epilepsy, EEG, interictal epileptiform activity, electrographic seizures

1. INTRODUCTION

Post-stroke seizure identification has many implications for clinical practice. On the one hand, epilepsy diagnosis can be made of a patient with at least one unprovoked seizure after stroke[93] since it has a recurrence probability of 71.5%[44]. On the other hand, although there is no quality evidence for the recommendation of acute symptomatic post-stroke seizures secondary prevention[148], this seems to be common in many centres in the acute stroke setting, to prevent additional metabolic burden[188].

However, the reported frequency of seizures after an ischaemic stroke is variable (2-67%)[21] possibly due to different study methodologies. One limitation of this frequency analysis has been the lack (in the vast majority of studies) of an electroencephalographic record[27]. In a retrospective study of acute brain injury patients submitted to EEG monitoring, most seizures (92%) were electroencephalographic without apparent clinical manifestations[75]. More specifically, 9% of patients with an acute ischaemic lesion had non-convulsive seizures and 7% had criteria for non-convulsive *status epilepticus*[75]. Thus, in the absence of an EEG record, the frequency of post-stroke seizures may be underestimated. Moreover, the frequency of electrographic seizures in patients with ischaemic stroke who do not require admission to an intensive care unit and EEG monitoring is unknown, although epileptic seizures[44,45] and ictal/interictal EEG discharges have been associated with stroke unfavourable outcome[46–48].

This paper aims to prospectively describe and compare the frequency of EEG and clinical epileptic manifestations in patients with an anterior circulation ischaemic stroke admitted to a Stroke Unit.

2. METHODS

Prospective study of consecutive patients with an acute anterior circulation ischaemic stroke, admitted to the Stroke Unit of a Neurology Department over a period of 24 months (between October 2011 and October 2013) and followed-up for 12 months (October 2012 to October 2014). The study was approved by the Ethics Committee of Centro Hospitalar Lisboa Norte ("Comissão de Ética para a Saúde").

The following inclusion criteria were used:

(1) Acute anterior circulation ischaemic stroke, established by imaging (CT scan or MRI) obtained at any time during hospitalization (reviewed by a senior neuroradiologist), with less than 7 days of clinical evolution

(2) National Institutes of Health Stroke Scale (NIHSS) score[70] ≥ 4 upon admission to the emergency department

(3) Signed informed consent by the patients or their next-of-kin.

The subsequent **exclusion criteria** were used:

(3) Previous stroke with modified Rankin scale score (mRS)[236–238] > 1 at the time of acute stroke

(4) Brain imaging study (CT scan or MRI) with one of the following: contusion; subdural/epidural hematoma; subarachnoid haemorrhage; neoplastic lesion; infectious/inflammatory lesion; hydrocephalus

(5) Previous history of head trauma with hospital admission

(6) Previous neurosurgery

(7) Previous history of epilepsy or epileptic seizures

2.1. Standardized clinical and ancillary evaluation

All patients were attended by a neurologist at the emergency department and admitted at the Stroke Unit with continuous surveillance of their neurological status and daily observation by a stroke neurologist. During hospitalization, the patients underwent diagnostic tests allowing stroke etiological classification[239] and appropriate therapeutic approach, including blood tests, carotid and vertebral duplex scans, transcranial Doppler and ECG. All patients underwent a CT scan at the emergency department (1st CT scan) which was repeated 24

hours after stroke in patients submitted to intravenous thrombolysis with alteplase (rtPA) and when clinically indicated in all patients (2nd CT scan). In selected cases, patients also performed MRI with diffusion weighted imaging, transthoracic or transesophageal echocardiography, 24h Holter or cerebral angiography. NIHSS score at hospital admission, after rtPA perfusion, daily and at discharge was registered prospectively (CB and HM). During hospitalization, the following clinical, laboratory and treatment variables were recorded daily: fever / infection (respiratory, urinary, other) / organ failure (kidney, liver, heart) / withdrawal syndrome / hydroelectrolytic imbalance / hypoxemia / seizure occurrence / other medical or neurological complication / pharmacological therapy (CB and HM).

After discharge the patient maintained standard clinical follow-up at the cerebrovascular outpatient clinic. A neurologist with expertise in epilepsy (CB) performed a telephone interview 6 months after stroke accessing seizure occurrence by a free interview followed by a brief phone screening tool for identifying patients with epilepsy[240]. A scheduled appointment 12 months after stroke was also conducted (CB), recording the following clinical variables: NIHSS and mRS scores, occurrence of seizures and its type; other stroke or medical complications; final etiological classification of stroke[239] and on-going therapy.

2.2. Neurophysiological Evaluation

All patients underwent a neurophysiological evaluation protocol that included a 64 channel video-EEG with a maximum duration of 60 minutes in different time frames after stroke:

(1) As early as possible, in the first 72 hours after admission (1st EEG)

(2) Daily, after the 1st EEG, for the first 7 days after stroke (except on weekend)

(3) If neurological worsening unexplained by medical complications and with indication for repeating the imaging exam.

EEGs referred in (2) and (3), were called serial EEG study during hospitalization

(4) At time of clinical discharge (discharge EEG)

(5) At 12 months after stroke (12M EEG)

The EEG record followed national and international recommendations [3,207–210]. Video-EEG was performed using a Nihon-Kohden device (Neurofax EEG-1200) with a sampling frequency of 1000 Hz. We used international 10/10 electrode placement system and recorded at least 64 EEG channels. The total recording period was at least 35 minutes of wakefulness, including activation tests. Sleep was recorded whenever possible at the end of the exam. All records were performed by neurophysiology technicians with expertise in video-EEG and EEG records in acute brain lesion patients. Further technical specifications and EEG protocol

can be read in **Appendix D**.

2.3. Imaging Interpretation

All imaging exams performed during the study period were reviewed by 2 senior neuroradiologists (CC and CM), blinded for clinical and electroencephalographic findings and trained for ASPECTS classification [241]. Doubts were discussed by consensus.

In patients with an infarct limited to the middle cerebral artery (MCA) territory in the imaging study (considering 1st CT scan, 2nd CT scan or MRI), the infarct size was quantified by ASPECTS[42] in 1st and 2nd CT scan. Insula and M1 to M6 ASPECTS territories were considered "cortical territories of ASPECTS". Furthermore, any type of haemorrhage transformation[242], cortical or subcortical infarct location, presence of cortical areas with normal attenuation coefficient (islands of preserved cortex) within the infarct[165,243,244] were evaluated in 2nd CT.

2.4. Operational definitions

2.4.1. Epileptic seizures and *status epilepticus* (only the first event was considered), were defined as:

- Epileptic seizure: clinical[93] and/or electrographic seizure[212,245]
- Acute symptomatic seizure: seizure occurring within the first 7 days of a stroke[142]. In these patients, cut-off values for metabolic disorders and febrile symptomatic seizures were not overreached and alcohol/drug withdrawal or intoxication[142] were excluded.
- Unprovoked seizure: seizure occurring after 7 days of a stroke in the absence of precipitating factors
- Epilepsy: occurrence of one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years[93]. The occurrence of at least one unprovoked seizure after stroke meets these criteria[44]
- *Status epilepticus*: ILAE classification[246] and Salzburg Consensus Criteria for Non-Convulsive *Status Epilepticus* (NCSE)[245,247]

2.4.2. Electroencephalographic abnormalities:

2.4.2.1. Occurrence in the 1st EEG of:

- Interictal epileptiform activity (IEA)[211]; EEG transients distinguishable from background activity with a characteristic spiky morphology, namely sharp waves (duration of 70-200 msec) and spikes (duration of 20-70 msec)
- Periodic discharges (PD)[212]; repetition of a waveform (with no more than 3 phases or any waveform lasting ≤0.5 seconds regardless of number of phases) with relatively uniform morphology and duration with a quantifiable inter-discharge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals
- Electrographic seizures[212,245]; generalized spike-wave discharges at 3/s or faster or clearly evolving discharges of any type that reach a frequency >4/s, whether focal or generalized. Evolving was defined as at least 2 unequivocal, sequential changes in frequency, morphology or location lasting for at least 3 cycles each. Evolution in frequency was defined as at least 2 consecutive changes in the same direction by at least 0.5/s. Evolution in morphology was defined as at least 2 consecutive changes to a novel morphology. Evolution in location was defined as sequentially spreading into or sequentially out of at least two different standard 10-20 electrode locations

2.4.2.2. Any EEG during hospitalization (1st EEG or serial EEG study during hospitalization) with IEA and/or Electrographic seizures

2.5. Statistical analysis

A descriptive analysis was used for nominal qualitative and quantitative (discrete and continuous) variables. Nominal variables are expressed in frequency, the discrete variables as medians and interquartile ranges (IQR) and continuous variables as means and standard deviations (SD).

Statistical analysis was done using SPSS program version 24 for Mac.

3. RESULTS

151 patients (112 men and 39 women) with an acute anterior circulation ischaemic stroke and a mean age of 67.4 (SD 11.9) years were included. Study flowchart is in **Figure 8**. Demographic, clinical and imaging characteristics of these patients are displayed in **Table 7**.

Figure 8. Study flowchart

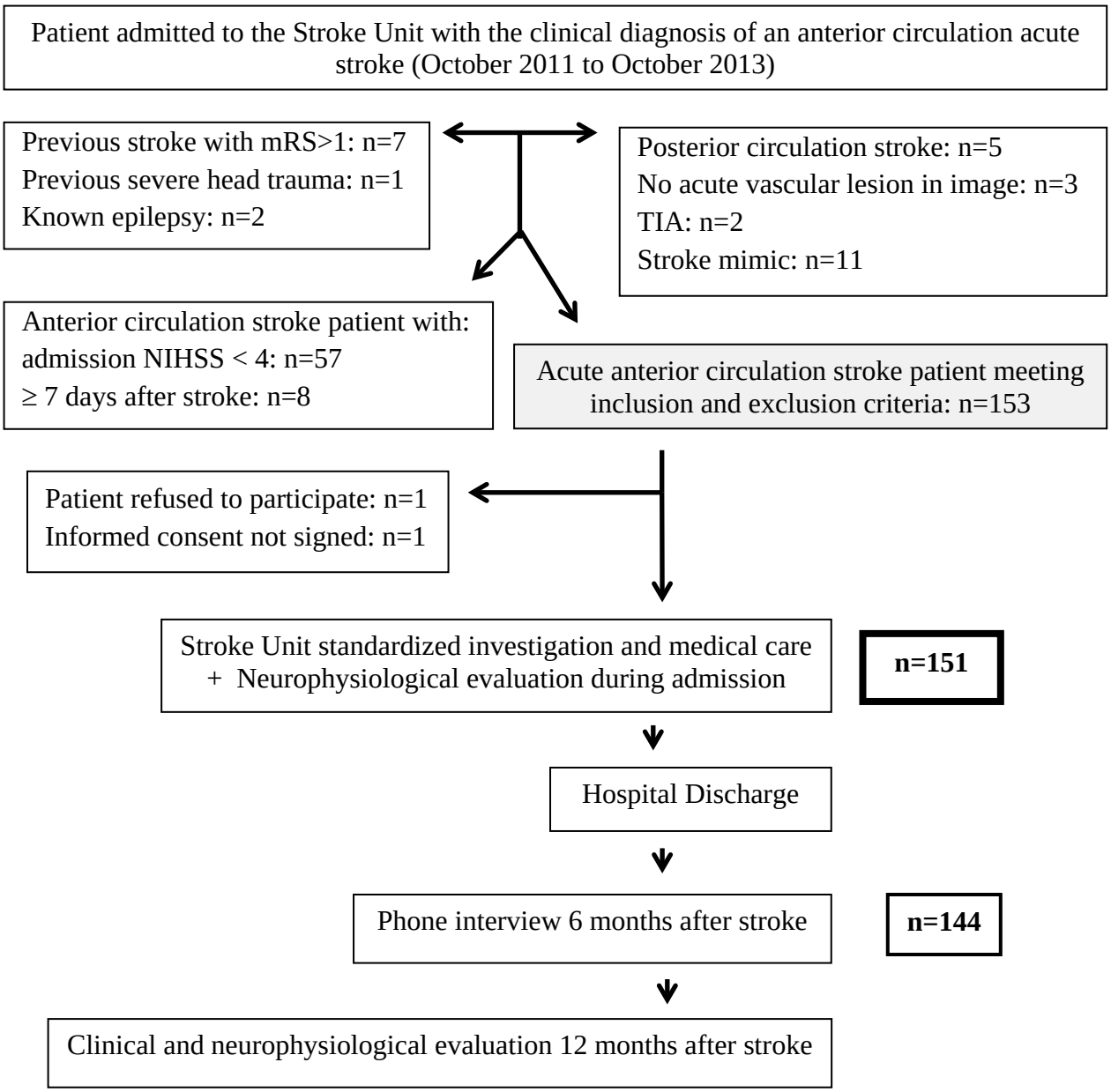

Table 7. Demographic, clinical and imaging characteristics of anterior circulation stroke patients

Demographic and clinical characteristics (n=151)	
Number of male / female patients (%)	112 / 39 (74.2% / 25.8%)
Mean age (SD[a])	67.4 (11.9)
Median NIHSS[b] at admission (IQR[c])	12 (10)
Number of patients treated with intravenous alteplase (%)	101 (67.3%)
Stroke aetiology: Cardioembolism	77 (51.0%)
Large-artery atherosclerosis	37 (24.5%)
Small-vessel occlusion	4 (2.6%)
Undetermined aetiology	29 (19.2%)
Other determined aetiology	4 (2.6%)
Medical complications / infections during hospitalization (%)	39 / 32 (25.8% / 21.2%)
Median time of hospitalization in days (IQR)	7 (6)
Median NIHSS at discharge (IQR)	6 (10)
Median NIHSS at 12 months (IQR)	3 (7)
mRS[d]≤2 at discharge	52 (34.4%)
mRS≤2 at 6 months	71 (47.0%)
mRS≤2 at 12 months	73 (48.7%)
mRS = 6	23 (15.2%)
Before the 7th day	7
Between the 7th day and the 6th month	11
Between the 6th and the 12th month	5

Imaging stroke characteristics (n=151)	
Vascular territory:	
ACA[e] isolated infarct	3 (2.0%)
ACM[f] isolated infarct	146 (96.7%)
Simultaneous ACA and ACM infarct	2 (1.3%)
Median 1st CT[g] ASPECTS[h] (IQR)	9 (3)
Median 1st CT Cortical ASPECTS[i] (IQR)	6 (3)
Characteristics of isolated MCA infarct in patients with a 2nd CT[j] scan (n=124)	
Location:	
Number of exclusively cortical infarcts	42 (33.9%)
Number of cortico-subcortical infarcts	56 (45.2%)
Number of exclusively subcortical infarcts	22 (17.7%)
Median 2nd CT ASPECTS (IQR)	6 (4)
Median 2nd CT cortical ASPECTS (IQR)	4 (4)
Other features of the 2nd CT scan (n=129)	
Number of patients with islands of preserved cortex within the infarct	26 (20.2%)
Number of patients with any type of haemorrhage transformation (%)	23 (17.8%)

Legend to table 7: [a]SD - Standard Deviation; [b]NIHSS - National Institutes of Health Stroke Scale score; [c]IQR - Interquartile range; [d]mRS - modified Rankin Scale; [e]ACA - Anterior Cerebral Artery; [f]MCA - Middle Cerebral Artery; [g]1st CT - 1st CT scan obtained at the emergency department; [h]ASPECTS - Alberta Stroke Program Early CT Score; [i]Cortical ASPECTS - Score in ASPECTS considering only the 7 cortical territories of this scale; [j]2nd CT - CT scan obtain ≥ 24 h after the infarct

All patients performed at least one EEG during hospitalization. The 1st EEG was performed in a median time of 1 day (IQR 1). The median number of tests performed per patient was 5 (IQR 3).

Of the 144 discharged patients, 143 patients (99.3%) underwent an EEG on this date. One patient (0.7%) refused the exam. The discharge EEG was made on average 11.1 (10.9) days after stroke (median 7).

Of the 127 patients who were alive at 12 months, 117 (92.1%) performed an EEG at this time and 10 patients (7.9%) refused to repeat the exam. One patient (0.66%) was lost for clinical and neurophysiological follow-up between month 6 and 12.

3.1. Epileptic manifestations frequency

In this study, 27 patients (17.9%) had EEG epileptiform activity (interictal epileptiform activity and/or Electrographic seizures) during hospitalization. **Table 8** shows the frequency of studied electroencephalographic abnormalities.

Table 8. EEG abnormalities in different time frames after stroke

	1st EEG[a] n (%)	**Serial EEG study during hospitalization[b]** n (%)	**Mc.Nemar´s test 1[c]** p	**Discharge EEG[d]** n (%)	**Mc.Nemar´s test 2[e]** p	**12M EEG[f]** n (%)	**Mc.Nemar's test 3[g]** p
Total of patients with:	151 (100%)	151 (100%)	-	143 (94.7%)	-	116 (76.8%)	-
PD[h]	27 (17.9%)	38 (25.2%)	0.007	9 (6.3%)	0.002	3 (2.6%)	0.002
IEA[i]	16 (10.6%)	18 (11.9%)	ns[l]	12 (8.4%)	ns	5 (4.3%)	ns
EEG seizures[j]	1 (0.7%)	6 (4.0%)	ns	0	ns	0	ns
NCSE criteria[k]	2 (1.3%)	2 (1.3%)	ns	0	ns	0	ns

Legend to table 8: [a]1st EEG - video-EEG (<60 minutes) performed in the first 72 hours after admission for acute anterior circulation ischaemic stroke; [b]Serial EEG during hospitalization - video-EEG (<60 minutes) performed daily for the first 7 days after stroke or if neurological worsening unexplained by medical complications and with indication for repeating the imaging exam (at least one EEG record during the hospitalization with one of the analysed features); [c]Mc. Nemar´s test 1 - Mc. Nemar´s test defining the difference between 1st EEG and serial EEG during hospitalization; [d]Discharge EEG - video-EEG (<60 minutes) performed at clinical discharge; [e]Mc. Nemar´s test 2 - Mc. Nemar´s test defining the difference between 1st EEG and discharge EEG; [f]12M EEG - video-EEG (<60 minutes) performed at 12 months after stroke; [g]Mc.Nemar´s test 3 - Mc. Nemar´s test defining the difference between 1st EEG and 12 months EEG; [h]PD - Periodic discharges; [i]IEA - interictal epileptiform activity; [J]EEG seizures - Electrographic seizures; [k]NCSE - Non-convulsive *status epilepticus*. Four patients (2.6%) had NCSE criteria during hospitalization. Of these, 3 had Electrographic seizures and one patient periodic discharges ≥ 3Hz in the 1st EEG; [l]ns - non-significant ($p > 0.05$)

Daily repetition of the EEG up to the 7th day after stroke allowed the identification of 6 more patients with electrographic seizures not shown in the 1st EEG. Clinical and imaging characteristics of patients with electrographic seizures during hospitalization are displayed in **Appendix E**. NCSE was diagnosed in 3 out of the 7 patients with electrographic seizures (42.8%) and to these patients anti-epileptic drugs were prescribed. The first electrographic seizure occurred until the 3rd day after stroke in 85.7% of patients (in 5 patients on the 2nd day and in 2 patients on the 3rd and 6th day after stroke, respectively).

The frequency of clinical and electroencephalographic epileptic manifestations is displayed in **Table 9**.

One year after stroke, 23 (15.2%) patients with an acute anterior ischaemic stroke had epilepsy diagnosis criteria. Seven of these epilepsy patients (30.4%) had had an acute symptomatic seizure in the first 7 days after stroke, 2 of which (28.6%) were exclusively electrographic seizures. Also, 31.8% of patients with acute symptomatic seizures (7 out of 22) also had an unprovoked seizure and consequently an epilepsy diagnosis.

In the first week after stroke, 4 patients (2.6%) had criteria for the diagnosis of NCSE [245,246]. In 2 of them, this diagnosis was made on the 1st EEG performed on the 2nd day after stroke and on other 2 during the first week EEG serial study (on the 3rd and the 6th day after stroke). Of the patients who met criteria for this diagnosis at the time of the 1st EEG, one had a fluctuating aphasia and periodic discharges at 3.5Hz (NCSE without coma, focal, aphasic) and another had consciousness impairment on the 2nd day after stroke, neither explained by imaging nor by medical complications and electrographic seizures, condition which reverted with antiepileptic treatment (NCSE without coma, focal, with impaired consciousness). Of the 2 other patients who were in NCSE in the first week after stroke, 1 had repeated sensitive focal seizures, an EEG with periodic discharges at 2 Hz and electrical seizures with clinical and neurophysiological recovery after levetiracetam (NCSE without coma, focal, without impairment of consciousness, with sensory symptoms). The last patient who was in NCSE during hospitalisation had a malignant infarction with consciousness impairment (coma Glasgow scale score = 4) and multiple seizures in the electroencephalographic recording (NCSE with coma).

Table 9. Frequency of clinical and EEG epileptic manifestations in anterior circulation stroke patients

Type of epileptic manifestation	**n (%)**
At least one epileptic seizure in the first year after stroke	**38 (25.2%)** - 33 (86.8%) exclusively clinical seizures - 5 (13.2%) exclusively electrographic seizures[a]
Acute symptomatic seizure (at least one)	**22 (14.6%)** - 17 (77.3%) exclusively clinical seizures - 5 (22.7%) exclusively electrographic seizures - 13 (59.1%) occurred in the first 24 hours
Unprovoked seizure as the first seizure	**16 (10.6%)**
Unprovoked seizure (at least one unprovoked seizure, with or without a previous acute symptomatic seizure)	**23 (15.2%)** - 7 also acute symptomatic seizures (5 clinical and 2 electrographic seizures) - 11 (47.8%) between day 7 and 6th month - 12 (52.2%) between the 6th and 12th month
IEA[a] in the 1st EEG	**16 (10.6%)**
Electrographic seizure within the first 7 days of stroke	**7 (4.6%)**
IEA or electrographic seizure during hospitalization	**27 (17.9%)**

Legend to table 9: [a] IEA - Interictal epileptiform activity

4. DISCUSSION

In this work, 18% of anterior circulation ischaemic stroke patients had interictal or ictal epileptiform activity in the EEG during hospitalization and 25% at least one seizure in the first year after stroke. Furthermore, more than 20% of acute symptomatic seizures were exclusively electrographic and more than 40% of patients with electrographic seizures had NCSE criteria or unprovoked seizures. Our results support the hypothesis that in the absence of a neurophysiological evaluation, the frequency of acute symptomatic seizures after stroke is underestimated.

Several strengths are identified in this work including the sample size of anterior circulation acute stroke patients, with prospective clinical and EEG follow-up, unlike previous studies (**Appendix F and G),** and the small number of patients lost for clinical follow-up (n=1). Another aspect that stands out is the use of internationally recognized terminology for EEG description[212]. This terminology not only shows a good inter-observer agreement[248,249] but it is recommended for multicentre research on EEG patterns in acute neurological disease patients[248] and for implementation in clinical practice[249]. Also, the time period for classification of seizures as acute symptomatic or unprovoked is in accordance with the ILAE recommendations[142] and only acute anterior circulation infarcts established by imaging were included.

There are some limitations in this study. The serial and non-continuous nature of the neurophysiological assessment may in fact be considered a constraint. However, using a single EEG with less than 60 minutes duration we found the same percentage of patients with periodic discharges and epileptiform activity as Carrera et al[29] in patients undergoing continued EEG monitoring for over 17 hours. Thus, our work suggests that a briefer EEG, performed in a short time window after stroke, can provide similar information than a longer record, with the advantage of being technically easier and less expensive. Nevertheless, periodic discharges and epileptiform activity have different specificities in seizure prediction. Although periodic discharges have been described in the continuum between an interictal and ictal phenomenon[250], this activity may be an acute cerebral lesion signature[251]. For this reason, we clearly defined and distinguished interictal epileptiform activity and periodic discharges. Nevertheless, the percentage of interictal epileptiform activity found in our study is not too different from Carrera et al.[29] (10.6% vs. 14%). Future studies should

compare the performance of short duration (spot) EEG *versus* a continuous one in the detection of epileptic manifestations.

In our series, 22.7% of acute symptomatic seizures were exclusively electroencephalographic and occurred for the first time in the majority (85.7%) of patient in the first 72 hours after stroke. An intensive care unit study, with continuous EEG also showed that 89% of seizures occurred within 72 hours[252]. These observations show the importance of a neurophysiological evaluation, particularly in the first 3 days after stroke. Furthermore, in our study, almost 1/3 (31.8%) of patients having a seizure in the first seven days after stroke had an epilepsy diagnosis one year after stroke, in accordance to Hesdorffer et al.[44] which found a 33% risk of an unprovoked seizure in patients with a first post-stroke acute symptomatic seizure. Additionally, our results showed that more than ¼ (28.6%) of post-stroke acute symptomatic seizure patients who had a vascular epilepsy diagnosis in a one-year time period, would not have been identified without the EEG protocol that was used.

However, in our study, the frequency of electrographic seizures (4.6%) is lower than that reported in continuous EEG studies in ischaemic stroke ranging between 6 to 27%[29,75,252–256] (**Appendix F**). This observation was expected since, compared with the 1st short duration EEG, a continuous record detected twice more seizures in a population of intensive care unit patients[254]. Nevertheless, it is possible that the low number of patients with electrographic seizures is not exclusively due to a shorter EEG duration but also to our study setting (a Neurology Department Stroke Unit) and to the inclusion of less severe stroke patients than intensive care units. Furthermore, different definitions of ictal epileptic activity can also account for the lower amount of detected Electrographic seizures in our study. The evidence favouring continuous *versus* spot EEG in detecting seizures is limited[76], especially in patients with ischaemic stroke admitted to non-intensive profile services as was the case of our patients. Still, continuous EEG it is not accessible at all centres and its cost-benefit is not determined[257].

In our study, 42.9% of patients with electrographic seizures fulfilled criteria for the diagnosis of NCSE or had unprovoked seizures in the clinical follow-up. In fact, non-convulsive *status epilepticus* has been described as one of the major diagnostic and therapeutic challenges in modern Neurology[258] and the EEG is essential for its diagnosis. The described association between post-stroke *status epilepticus* and functional prognosis[81,82,259], reinforces the

importance of early recognition of this entity, allowing appropriate and timely treatment. Due to very low clinical evidence, current ESO guidelines[148] only give weak recommendations on secondary prevention of acute symptomatic post-stroke seizures. Their treatment is frequently decided on an individual basis depending on the presence of an altered mental status, fluctuating neurological recovery or criteria for the diagnosis of *status epilepticus*[188]. In our study, more than 40% of patients with Electrographic seizures had NCSE criteria and 75% of patients with NCSE (3 out 4) had no obvious clinically acute post-stroke symptomatic seizures, showing the usefulness of our electrophysiological study.

VII. PROJECT 4

"To differentiate from the ordinary cortical epilepsia, it may be called *epilepsia corticalis sive partiallis*, in that the convulsive manifestations are continuous"

Aleksei Yakovlevich Kozhevnikov (1894)

EPILEPSIA PARTIALIS CONTINUA AFTER AN ANTERIOR CIRCULATION ISCHAEMIC STROKE

AUTHORS

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ABSTRACT

Background and purpose: Although cerebrovascular disorders are the main cause of *Epilepsia Partialis Continua* (EPC) in adulthood, the frequency of EPC after stroke is unknown. The aim was to prospectively ascertain its frequency one year after an ischaemic stroke.

Methods: This was a prospective study of consecutive acute anterior circulation ischaemic stroke patients, previously independent with an admission NIHSS score ≥ 4, an acute ischaemic lesion on imaging and no previous seizures. During admission patients received standardized diagnostic and medical care and were submitted to a neurophysiological evaluation protocol. One year after stroke, patients were re-evaluated by an epilepsy expert neurologist and performed video-EEG with EMG co-registration whenever myoclonus was observed during neurological examination for jerk-locked back-average analysis (JLBA). EPC was defined as continuously repeated fragments of epileptic seizures, with preserved consciousness, lasting at least 1h, and representing locally restricted epileptic activity.

Results: In all, 151 acute anterior circulation stroke patients were consecutively included, and prospectively evaluated, but 23 died in the first year. One year after stroke, from 127 patients alive, 117 (92.1%) underwent clinical and neurophysiological evaluation. In 2 (1.7%) patients, EPC diagnosis was made both by clinical and electroencephalographic criteria, namely JLBA. Both patients had a history of unprovoked seizures and one of them acute symptomatic seizures and non-convulsive *status epilepticus* criteria during the first 7 days after stroke.

Conclusions: Despite its low frequency, the high stroke incidence makes post-stroke EPC relevant. This study draws attention to this recognizable condition with therapeutic and eventually prognostic implications.

KEY-WORDS

Epilepsia partialis continua, *status epilepticus*, jerk-locked back-average analysis, cortical myoclonus, stroke, cerebral infarction

1. INTRODUCTION

Cerebrovascular disorders are the main cause of *Epilepsia Partialis Continua* (EPC)[260,261] in adulthood. However, to our knowledge, the frequency of this type of focal *status epilepticus*[246] as a chronic post-stroke complication in large series, has not been reported. Our hypothesis is that the subtle clinical signs in motor EPC make this disorder under recognised.

In this study, we aim to describe the frequency of this entity, one year after an anterior circulation ischaemic stroke.

2. METHODS

Prospective study of consecutive patients admitted to our Stroke Unit from October 2011 to October 2013, with an acute anterior circulation ischaemic stroke. The Ethics Committee "Comissão de Ética para a Saúde" of the HSM-CHLN approved this study. Signed informed consent was obtained from all patients or their next-of-kin.

Patients had to be previously independent (modified Rankin scale score <1), have an NIHSS score ≥ 4 at hospital admission and an acute ischaemic lesion identified by brain imaging (CT or MRI). Exclusion criteria were a previous history of epileptic seizures, traumatic head injury requiring hospital admission or brain surgery.
Included patients were submitted to standard cerebrovascular clinical and complementary evaluation during admission and after discharge. Seizure occurrence during the first year after stroke was prospectively quantified and seizures were classified as acute symptomatic[142] or unprovoked[145] whenever they occurred within the first 7 days after stroke or after that time point in the absence of precipitating factors, respectively.

All patients underwent a neurophysiological evaluation protocol that included a 64 channel video-EEG with a maximum duration of 60 minutes in the first 72h after stroke, during admission (daily until day 7 and after that if neurological worsening), at discharge and one year after stroke.

A neurologist with expertise in epilepsy (CB) made a phone interview 6 months after stroke, accessing seizure occurrence by a free interview followed by a brief phone screening tool for identifying patients with epilepsy[240] and a scheduled appointment 12 months after the cerebrovascular event. On this occasion neurological examination was always performed and special attention was given to the observation of face and limbs at rest, and to the performance of myoclonus activation manoeuvres such as posture maintaining, passive mobilization and tactile stimulation. On the same day as this appointment, a video-EEG with a sampling frequency of 1000 Hz, at least 64 channels placed according to the 10/10 international system and 60 minutes maximum duration was performed. Whenever myoclonus was observed during the neurological examination, synchronized EMG record of the involuntary movement was added to the exam. The EEG record included eye-lid opening and closure, hyperventilation, photic stimulation and manoeuvres to elicit

myoclonus, as previously observed in the neurological medical evaluation. Experienced technicians under medical supervision performed the EEG. The procedure allowed subsequent offline "jerk-lock back-average". This analysis was performed using the BESA software, version 6.0 with the aim of looking look for an electroencephalographic transient temporally related to the involuntary movement. The identification of a wave, with a coherent focal localization and a short latency to a myoclonus burst, lasting less than 100 ms, was considered an argument for a cortical correlate of the registered myoclonus[262].

Primary outcome of this study was the presence of *epilepsia partialis continua* defined as a condition of continuously repeated fragments of epileptic seizures (motor or sensory), with preserved consciousness, lasting at least 1 h, and representing locally restricted epileptic activity[263]. The presence of a cortical correlate in "jerk-lock back-average" of suspect clinical motor phenomena was considered as evidence of motor cortex hyperexcitability, supporting the diagnosis of EPC.

3. RESULTS

In all, 151 patients (112 men and 39 women) with an acute anterior circulation ischaemic stroke were included, with a mean age of 67.4 (SD 11.9) years.

In 146 patients (96.7%) the acute imaging lesion was limited to middle cerebral artery (MCA) territory and in 3 (2.0%) to anterior cerebral artery (ACA) territory. Furthermore, in 2 patients both ACA and MCA territories were involved. In a brain CT scan performed at least 24 hours after stroke, median ASPECTS[42] was 6 (IQR 4) and median ASPECTS considering only the 7 cortical territories of this scale was 4 (IQR 4). The percentage of patients with middle cerebral artery territory limited stroke patients with involvement of each of ASPECTS territories is disclosed in **Appendix H**.

In the first year after stroke, 23 patients had died (seven during admission and 16 after discharge) and one patient was lost to follow-up after the 6 months telephone interview. At 12 months after stroke, 127 patients were alive and 117 (92.1%) agreed to come to the scheduled clinical appointment and underwent an EEG.

At the one-year appointment, two patients (1,7%), both with previous acute symptomatic and/or unprovoked sensorimotor seizures (**Table 10**), presented with continuous and subtle involuntary movements of the upper limb contralateral to the ischaemic lesion, not spontaneously reported by the patient nor their family. Several fingers showed irregular, small amplitude, non-synchronized subtle and mainly jerky movements, suggesting described central minipolymyoclonus[264]. The involuntary movement semiology is shown in **video 1 and 2** (**Appendix I and J**, digital only - https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.13310). A cortical correlate of the aforementioned involuntary movements was found by jerk-lock back-average technique (**Figure 9**), adding neurophysiological criteria of *EPC* to clinical observation. In these patients, no epileptiform activity was detected in the raw EEG analysis. Clinical, imaging and neurophysiological characteristics, as well as the treatment of patients with EPC are described in **Table 10**.

In our series, sensory symptoms as a manifestation of EPC were not recorded.

Table 10. Clinical, imaging and neurophysiological characteristics of patients with post-stroke *Epilepsia Partialis Continua*

	Patient 1	**Patient 2**
Clinical features		
Age (years)	71	77
NIHSS[a] at admission	16	7
NIHSS[a] after intravenous alteplase	14	7
NIHSS[a] at discharge	12	8
Stroke aetiology after investigation	Undetermined	Undetermined
Acute symptomatic seizures[b] and its type	No	Yes Focal seizures (sensory) and non-convulsive *status epilepticus* criteria [247]
Unprovoked seizures[c] and its type	Yes Focal seizures (motor) of the left upper limb	Yes Focal seizures (motor) of the left limbs during sleep
Time of the 1st seizure	Between 6 and 12 months	3rd day after stroke
EPC[d] semiology (12 months after stroke)	Irregular, small amplitude, non-synchronized subtle mainly jerky movements of several fingers, accentuated by posture (video 1, online only)	Irregular, small amplitude, non-synchronized subtle jerky movements of several fingers, accentuated by posture (video 2, online only)
Anti-epileptic drugs	Levetiracetam started by the time of the EPC diagnosis	Levetiracetam started during admission, dose increased after EPC diagnosis
Modified Rankin scale score at 12 months	3	3

	Patient 1	Patient 2
Brain-CT scan[e] features		
Vascular territory	Right middle cerebral artery	Right middle cerebral artery
ASPECTS[f] (total score)	3	5
ASPECTS[g] (infarct location)	I, L, C, IC, M2, M3, M6	I, IC, M2, M3, M6
Any type of haemorrhage transformation	Yes	Yes
Islands of spared cortex within the infarct	Yes	No
Neurophysiological features		
Raw EEG analysis (performed 12 months after stroke)	Right fronto-temporal focal and rhythmic slow wave activity. No interictal epileptiform activity.	Right fronto-temporal focal slow wave activity. No interictal epileptiform activity
Jerk-locked back-average	A negative right central EEG transient preceding muscle activation (**Figure 9**)	A negative right central EEG transient preceding muscle activation (**Figure 9**)

Legend to table 10: [a]NIHSS, National Institute of Health Stroke Scale score (quantifying stroke clinical severity); [b]Acute symptomatic seizure, seizures occurring in the first seven days after stroke; [c]Unprovoked seizures, seizures occurring after the first seven days after stroke, in the absence of precipitating factors; [d]EPC: *Epilepsia Partialis Continua*; [e]Brain-CT Scan**,** brain CT Scan performed 24 hours after stroke; [f]ASPECTS - Alberta Stroke Program Early CT Score (quantifying infarct size and location in middle cerebral artery territory) ; [g]ASPECTS (infarct location) - I, insular ribbon; L, lentiform nucleus; C, caudate; IC, internal capsule; M1, anterior MCA cortex; M2, MCA cortex lateral to the insular ribbon; M3, posterior MCA cortex; M4, M5, M6, anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, rostral to basal ganglia.

Figure 9. Jerk-locked back-average analysis (JLBA)

Legend to figure 9:

Patient 1 **(a)** - JLBA analysis of 49 activations of the left *flexor digitorium superficialis*. There is a negative electroencephalographic transient starting 50 msecs before the onset of the EMG activation (arrows). Top view arrangement of the average montage (EEG recorded with: sensitivity=5 microV/mm; high frequency filter (HFF)=70 Hz, low frequency filter (LFF)=0.53; Notch filter (50 Hz) on).

Patient 2 **(b)** - JLBA of 259 activations of the left *abductor pollicis brevis*. There is a small amplitude negative electroencephalographic transient on the right central leads that starts 45msecs before the EMG activation (arrow). Top view arrangement of the average montage (EEG recorded with: sensitivity=5 microV/mm; HFF=70 Hz; LFF off; notch filter off). Montage was reduced to 9 channels due to frequent artefacts in the remaining.

4. DISCUSSION

In this study, the frequency of EPC as a remote complication of anterior circulation ischaemic stroke is very low. However, because stroke is a frequent neurological disorder, health professionals caring for patients with cerebrovascular disorders and aware of this disorder, will find EPC in a significant number of patients.

Epilepsia partialis continua can be classified as a focal motor *status epilepticus* type[246], although some authors extend the meaning of EPC to cover other type of focal seizures which are continuous without spreading to a larger seizure or with only occasional spread[263]. Its physiopathology is not completely understood but the hyperexcitability of the sensorimotor cortex, the presence of cortical generators and cortical-subcortical loops, can contribute to the persistence of a focal cortical epileptiform activity [265]. The biologic changes associated with post-stroke gliosis and meningocerebral cicatrix formation may result in hyperexcitability and neuronal synchrony[21] facilitating EPC.

The diagnosis of EPC frequently implies a high level of clinical suspicion and requires a careful clinical evaluation including myoclonus activation manoeuvres. In this prospective study, the subtle involuntary movements of the fingers were not reported by the patient and were only detected at clinical inspection, increasing with activation manoeuvres, resembling minipolymyoclonus[264]. Minipolymyoclonus of central origin was first described by Wilkins, Hallet & Erba in 1985[264] in 11 heterogeneous patients with different types of epilepsy syndromes and neurodegenerative disorders. To our best knowledge, this manuscript is the first to describe this phenomenology in a prospective cohort of stroke patients.

Clinical suspicion of EPC must be corroborated by imaging and neurophysiology studies[262], including jerk-lock back-average analysis, as in our patients. This neurophysiological technique is of utmost importance because raw data visual analysis does not necessarily show continuous or persistent epileptiform or periodic abnormalities, such as in other types of focal or non-convulsive *status epilepticus*[245,247]. However, we must reinforce that back-average analysis only confirms the cortical origin of the involuntary movement. The clinical integration of this data is essential to the EPC diagnosis, since cortical myoclonus and minipolymyoclonus can be found in other pathologies[262,264]. The two patients of our study also had sporadic unprovoked focal motor seizures supporting the diagnosis of this form of

status epilepticus. In fact, clinical phenomenology of EPC can be seen as continuously repeated fragments of motor seizures[263]. Furthermore, one of our patients had a diagnosis of non-convulsive focal *status epilepticus* without impairment of consciousness in the first week after stroke.

It should also be emphasised that, in stroke patients, involuntary movements can be caused by different mechanisms and that post-stroke focal myoclonus can additionally be a hyperkinetic movement disorder, where basal ganglia are most often involved. Although lesions in different parts of the brain can cause the same movement disorder, post-stroke myoclonus is usually associated with lesions in the midbrain, pons or thalamus and is frequently an acute stroke complication[266,267]. This was not the case of our patients. Furthermore, an involuntary movement cortical correlate was established in this work by back-average analysis.

Regarding treatment of EPC, studies that included patients with ischaemic stroke as the aetiology show the use of different anti-epileptic drugs and variable clinical response, frequently requiring polytherapy or even being refractory to medical therapy[260,261]. As in our study, Mameniskiene and collaborators' study showed that the control of EPC did not always correlate with control of other types of seizure in the same patient[263].

The consequences of post-stroke EPC are unknown although post-stroke epileptic phenomena (seizures and *status epilepticus*)[45,79–82] have been associated with a worse infarct outcome.

VIII. PROJECT 5

"Epileptic myoclonus is a transient (<100 ms), involuntary, muscle jerk due to abnormal excessive or synchronous neuronal activity in the brain"

Chrysostomos Panayiotopoulos (2010)

CORTICAL MYOCLONUS DURING IV THROMBOLYSIS FOR ISCHAEMIC STROKE

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ABSTRACT

We describe a patient with an acute middle cerebral artery ischaemic stroke developing subtle involuntary movements of the paretic upper limb with cortical origin during rtPA perfusion. Despite the multiple potential pathophysiological mechanisms for the relationship between thrombolysis and epileptic activity, seizures during this procedure are scarcely reported. Our hypothesis is that subtle and transient clinical seizures, like those described in our patient, may not be detected or are misdiagnosed as nonepileptic involuntary movements.

We aimed to draw attention to the recognition challenge of this paroxysmal motor behaviour, highlighting this clinical and neurophysiological identification using video recording and back-average analysis of the EEG.

KEY-WORDS

seizures, cerebral infarct, recombinant tissue-type plasminogen activator (rtPA), EEG, back-average analysis

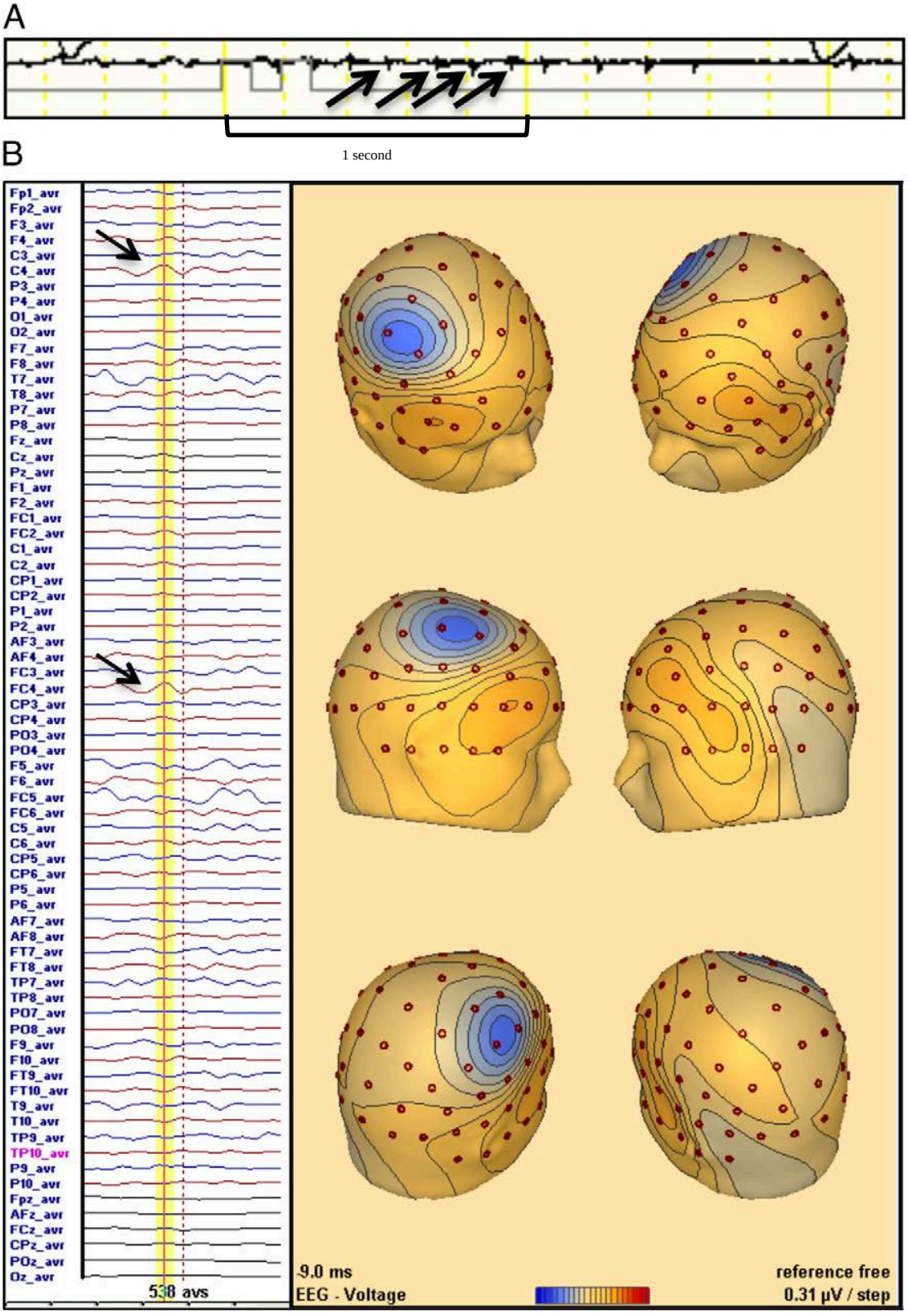
1. INTRODUCTION

Early post-stroke seizures (i.e. occurring within one week after stroke) are thought to result from cellular biochemical dysfunction leading to electrically irritable cerebral tissue. Intravenous thrombolysis (IVT) with recombinant tissue-type plasminogen activator (rtPA) is the gold standard treatment for acute ischaemic stroke, and, recently, Alvarez et al.[28] showed that this procedure may be independently associated with acute symptomatic seizures. However, and despite multiple potential pathophysiological mechanisms, seizures coincident with rtPA administration are seldom reported. Here, we describe a patient with an acute middle cerebral artery (MCA) ischaemic stroke who developed subtle involuntary movements of the paretic upper limb, with cortical origin as documented neurophysiologically, during rtPA perfusion. We aimed to draw attention to the recognition challenge of this paroxysmal motor behaviour, highlighting its clinical and neurophysiological identification using video recording and back-average analysis of the EEG.

2. CASE REPORT

A 72-year-old male with a past history of hypertension, dyslipidaemia, chronic kidney disease, and an ischaemic stroke 15 years ago, with no post-stroke seizures and from which he had completely recovered, presented to the emergency department with sudden onset of left central facial palsy, hemiparesis, homonymous hemianopia, and right gaze deviation (NIHSS score = 10). Electrocardiogram showed atrial fibrillation, and blood analysis revealed acute renal failure (creatinine = 4 mg/dL, blood urea nitrogen = 134 mg/dL). Plain head computed tomography (CT) disclosed old occipital, parietal, and frontal ischaemic lesions and a right middle cerebral artery (MCA) hyperdensity. Intravenous alteplase (rtPA) was started 140 min after symptom onset. Twenty minutes after starting the infusion period, involuntary movements of the upper paretic limb were noticed. The movements involved either the distal or the proximal muscles, independently, and could be jerk-like, irregular, myoclonic like, or slow and brief (**Video 3 - Appendix K**, digital only - http://dx.doi.org/10.1016/j.ebcr.2014.09.004). During rtPA perfusion, a 72-channel EEG (International 10/10 System) with an EMG channel recording the left flexor digitorum superficialis (sample frequency of 1000 Hz) captured brief, repetitive, and almost periodic muscle activations (**Figure 10A**). No epileptiform activity was apparent in the raw EEG data. Back-average analysis of the EEG time-locked with the onset of the recorded myoclonus (538 activations) was performed (BESA software, version 6.0), revealing a right frontocentral negative wave. This EEG transient preceded muscle activation by 30 ms (**Figure 10B**). No antiepileptic drug was given, and the involuntary movements lasted approximately 40 min, stopping by the end of the rtPA perfusion. The neurological deficit did not improve after thrombolysis. Transcranial Doppler showed no recanalization. Computed tomography at 24 h disclosed an acute MCA infarct scoring 5 on ASPECTS, with spared cortical areas within the infarct zone (**Figure 11**). The patient partially recovered after 7 days (NIHSS score=6). No further involuntary movements or clinically suspected seizures were observed despite transitory worsening of renal function during hospitalization. One year after stroke, the patient is alive and independent (NIHSS = 1 and mRS = 1), with no report of late post-stroke seizures.

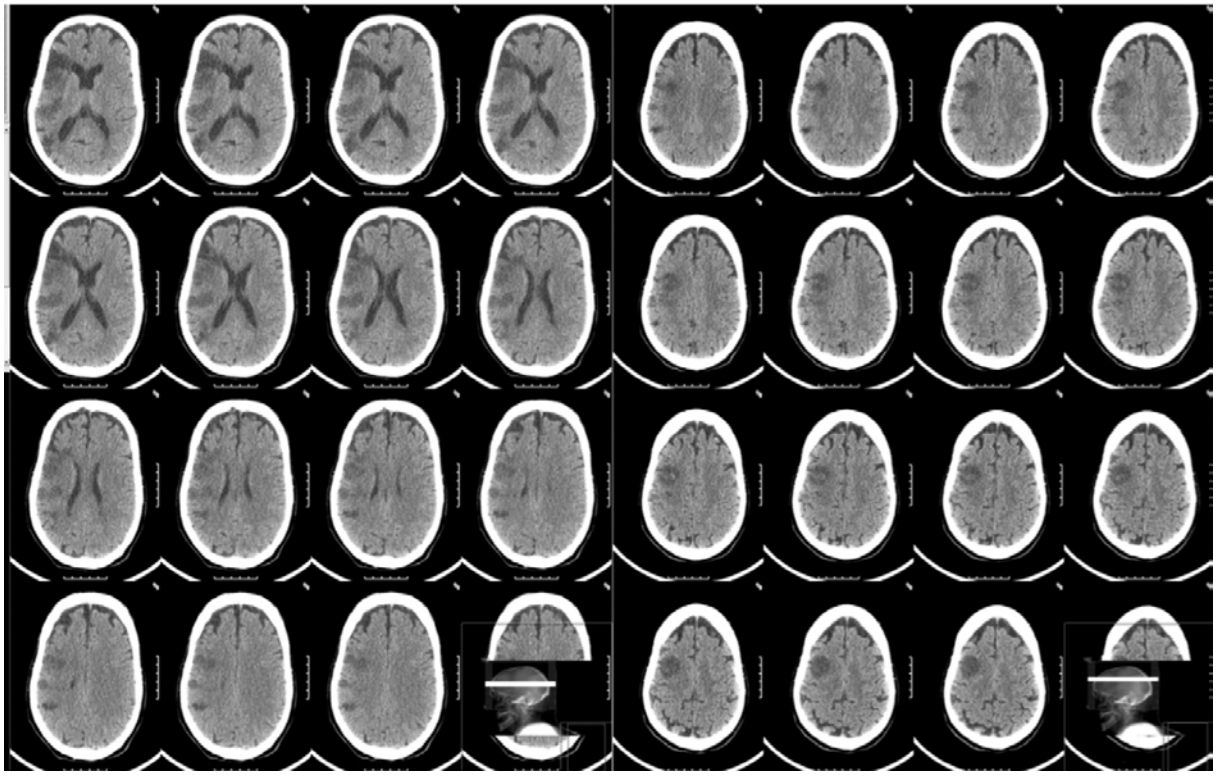
Figure 10. Back-average analysis



Legend to figure 10: A) EMG channel recording the left flexor digitorum superficialis capturing brief, repetitive, and almost periodic muscle activations (arrows). B) EEG back-average analysis disclosing a negative transient (arrows) with a peak (yellow line) of 10 ms

before EMG activations (dotted line) at right central electrodes (C4/FC4).

Figure 11. Brain CT scan



Legend to figure 11: Brain CT scan 24 h after intravenous alteplase disclosing an acute right MCA infarct, scoring 5 (I,M1,M2,M5,M6) on ASPECTS, with spared cortical areas within the infarct zone.

3. DISCUSSION

We report a patient with an acute MCA ischaemic stroke who developed subtle involuntary movements of the paretic upper limb, with cortical origin as documented neurophysiologically, during rtPA perfusion. Because cortical myoclonus and epileptogenic discharges are generated by neuronal hypersynchronous activities sharing the same physiopathogenic mechanisms, the recorded myoclonus can be considered an acute symptomatic seizure. Because of the subtleness of the movements, the clinical stability of the patient, and the absence of clear epileptiform activity on the immediate raw EEG analysis, no antiepileptic medication was given. Back-average analysis, enlightening the cortical origin of the myoclonus, was only performed after the acute phase.

Even though our patient had multiple risk factors for seizures (acute renal lesion, acute anterior stroke, cortical involvement), the close time relationship of this paroxysmal motor behaviour with the therapeutic intervention raises the possibility of an association. It has been documented that seizures during rtPA perfusion can occur even in the absence of a cerebral lesion, as described in 2 patients submitted to thrombolysis for acute myocardial infarction[30]. In fact, neurotoxic and epileptogenic properties[31] of rtPA are known. Other postulated mechanisms for seizures during thrombolysis for ischaemic stroke include secondary cortical infarct from distal embolization or reperfusion/hyperperfusion syndrome[32]. Despite the multiple potential pathophysiological mechanisms for the relationship between rtPA and seizures, the frequency of seizures during thrombolysis is not well known. Besides a few reports of overt seizures occurring in close proximity to rtPA perfusion[30,31], most larger studies looking at seizure frequency in patients submitted to thrombolysis report a global incidence of seizures within 7 days after stroke and not specifically during the therapeutic procedure. In these studies, patients submitted to thrombolysis have similar frequency of early seizures when compared with patients without thrombolysis. Only one study concluded that thrombolysis is an independent risk factor for early seizures after stroke[28]. These discrepancies may be related to the retrospective collection of the data. Additionally, reporting bias due to increased clinical vigilance in the acute phase of patients undergoing thrombolysis cannot be excluded. Finally, it is also possible that subtle and transient clinical seizures, like those described in our patient, may not be detected or are misdiagnosed as nonepileptic involuntary movements.

IX. PROJECT 6

"Thrombolysis has, to our knowledge, not been investigated as a risk factor for early seizures, despite its potential neurotoxic and possible epileptogenic effects in animals."

Vincent Alvarez et al. (2012)

EPILEPTIC MANIFESTATIONS IN STROKE PATIENTS TREATED WITH INTRAVENOUS ALTEPLASE

AUTHORS

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ABSTRACT

Background: Intravenous alteplase (rtPA) may be associated with seizures and epileptic activity in the electroencephalogram (EEG). We aimed to compare seizures and EEG abnormalities frequency between stroke patients treated and not treated with rtPA.

Methods: Prospective study of consecutive acute anterior circulation ischaemic stroke patients, with one-year follow-up. Patients were previously independent, had an admission National Institute of Health Stroke Scale score ≥ 4, an acute ischaemic lesion and no previous seizures. They received standardized diagnostic and medical care. Video-EEG was performed in 72h (1st EEG); during admission (daily until day 7 and after that if neurological worsening); at discharge and one year after stroke.

Results: In all, 151 patients (101 treated with rtPA) were included. Acute and unprovoked seizures frequency was not significantly different between rtPA treated and non-treated patients (p=0.726 and p=0.748, respectively). Clinical paroxysmal phenomena during rtPA perfusion were observed in 5 (5%) patients.

In the 1st EEG, rtPA treated patients had background diffuse slowing more often [43.6% vs. 26.0%, p=0.036]. This difference was no longer observed at discharge [24.0% vs. 19.1%, p=0.517] nor one year after [11.8% vs. 10.0%, p=0.765]. No differences were found in epileptiform (p=0.867) or periodic discharges (p=0.381) frequency.

Conclusions: rtPA is not associated with an increased risk of clinical or electroencephalographic epileptic phenomena.

KEY-WORDS

symptomatic seizures; epilepsy; stroke; alteplase; EEG; ASPECTS; outcome

1. INTRODUCTION

Thrombolysis is the *gold standard* of acute ischaemic stroke treatment. However, it has been suggested that intravenous alteplase (rtPA) is associated with clinical seizures and the occurrence of epileptic activity in the EEG[28,29]. Several physiopathological mechanisms can be postulated for this association, including cortical reperfusion/hyperperfusion syndrome[32], neurotoxicity and a possible epileptogenic effect of rtPA[31,32,77,78], or the survival of islands of cortical viable tissue[165]. Intravenous alteplase related seizures[30,32,33] and seizure frequency in patients treated with rtPA[34,35] has been mostly described using retrospective and non-controlled case series. Furthermore, the occurrence of seizures in rtPA patients has been associated with different stroke functional outcomes[28,32,34,35,172].

We aim to compare seizure frequency and electroencephalographic abnormalities between anterior circulation ischaemic stroke patients treated and not treated with rtPA and to know if post-stroke seizures are associated with functional outcome in these patients.

2. METHODS

A prospective longitudinal study of consecutive adult patients with an acute anterior circulation ischaemic stroke, admitted to the Neurology Department Stroke Unit of a University Hospital, between October 2011 and October 2013, and followed for 12 months. The Ethics Committee "Comissão de Ética para a Saúde" of the HSM-CHLN approved this study.

Included patients had to be previously independent [modified Rankin Scale (mRS) ≤1], score a value of at least 4 on National Institute of Health Stroke Scale (NIHSS) upon admission to the emergency department (ED), have had an acute ischaemic brain lesion in the internal carotid artery territory [in the computed tomography (CT) scan or magnetic resonance imaging (MRI)] and have no previous history of epileptic seizures nor traumatic head injury requiring hospital admission. All subjects or their next of kin gave written informed consent for participation in this study. Patients were treated with intravenous alteplase (rtPA) according to ESO guidelines[72]. Patients were not submitted to rtPA treatment if outside the 4.5-hour time window, in the presence of minor stroke (NIHSS < 4) or if showing contraindications to this drug. All patients received a standardized cerebrovascular disease investigation and medical care during admission and after discharge. A neurologist with expertise in epilepsy (CB), blinded to the neurophysiological evaluation, conducted a phone interview at six months after stroke accessing seizure occurrence by a free interview, followed by a brief phone screening tool for identifying patients with epilepsy[240]. A scheduled clinical appointment 12 months after stroke was also conducted (CB), recording the following clinical variables: NIHSS and mRS score, occurrence of seizures and its type; other stroke or medical complications; final aetiological classification of stroke[239] and ongoing therapy.

2.1. Neurophysiological evaluation

All patients underwent a neurophysiological evaluation protocol that included a 64 channel video-EEG with a maximum duration of 60 minutes in different time frames after stroke: in the first 72 hours (1st EEG), daily in the first 7 days after stroke, during admission after that time point if there was neurological worsening unexplained by medical complications, at discharge and 12 months after stroke.

The record included an eyes closed wake resting condition and eyes open, hyperventilation and photic stimulation manoeuvres. The EEG review and classification was performed by a

certified clinical neurophysiologist (CB) using international criteria and terminology [211,212,245], blinded for clinical and imaging findings. All doubts were decided by consensus with another clinical neurophysiologist (ARP).

2.2. Imaging interpretation

Two senior neuroradiologists (CM and CC), blinded for clinical and electroencephalographic findings, reviewed all imaging tests. Doubts were decided by consensus. In patients with an infarct limited to the middle cerebral artery (MCA) territory in the imaging study (considering 1st CT scan, 2nd CT scan or MRI), the infarct size was quantified by Alberta Stroke program Early CT Score (ASPECTS)[42], in a repeated brain CT scan performed 24 hours after stroke (2nd CT scan). ASPECTS in the 2nd CT scan was rated as 10 whenever an acute vascular lesion in the middle cerebral artery territory was only identified by MRI.

2.3. Predictors and Outcomes

The following characteristics were compared between patients treated and not treated with rtPA:

2.3.1. Demographic and stroke characteristics: age, gender, NIHSS [70] on admission and post-rtPA (if applicable) and stroke aetiology [239]

2.3.2. Imaging characteristics: exclusively cortical and subcortical infarct, ASPECTS[42], presence of normal attenuation coefficient cortical areas (islands of preserved cortex) within the infarct[165] and any intracerebral haemorrhage transformation[242]. Insula and M1 to M6 ASPECTS territories were considered “cortical territories of ASPECTS”.

2.3.3. Occurrence of epileptic seizures and *status epilepticus* (only the first event was considered), with the following operational definitions:

- Epileptic seizure: clinical [93] and/or electrographic seizure[212,245]
- Acute symptomatic seizure: seizure occurring within the first 7 days of a stroke[142]. In these patients, cut-off values for metabolic disorders and febrile symptomatic seizures were not overreached and alcohol/drug withdrawal or intoxication[142] were excluded
- Unprovoked seizure: Seizures occurring after 7 days of a stroke in the absence of precipitating factors[145]

- *Status epilepticus*: ILAE *status epilepticus* classification[246] and Salzburg Consensus Criteria for Non-Convulsive *Status Epilepticus*[245,247] were used

2.3.4. Electroencephalographic abnormalities:

- In the 1st EEG: background activity slowing[211]; asymmetry[212]; suppression (focal, hemispheric or diffuse)[212]; focal slow wave activity (FSWA), including focal and regional concept[211]; rhythmic slow wave activity (RSWA), including rhythmic delta activity defined by ACNS[212] and rhythmic delta/theta (>0.5 Hz)[245], Interictal epileptiform activity (IEA)[211]; periodic discharges (PD)[212]; electrographic seizure[212,245].
- Any EEG during hospitalisation with IED and/or electrographic seizures

2.3.5. Functional outcome: measured by modified Rankin Scale (mRS)[236]. Death or dependency (mRS ≥ 3) at discharge and 12 months after stroke was considered an unfavourable outcome

The primary outcome of this study was the occurrence of epileptic seizures and EEG abnormalities.

2.4. Statistical Analysis

We compared demographic and stroke characteristics, imaging and EEG findings, epileptic seizure frequency and functional outcome, in patients treated or not treated with rtPA.

In patients with post-stroke seizures age, admission NIHSS, ASPECTS and functional outcome at 12 months were compared between rtPA treated and not treated patients. Functional outcome at 12 months was also compared between patients with and without seizures in both groups.

Bivariate analysis of qualitative variables was performed by the chi-square test, Fisher's exact test or the McNemar test, and quantitative variables by the t-test or Mann-Whitney U, as appropriate.

Significant bivariate analysis findings were adjusted for age, clinical (admission NIHSS) and imaging (ASPECTS) severity, in a logistic regression model. The calibration of the model was analysed by the Hosmer-Lemeshow test and its discriminative capacity measured by the area under the receiver operating characteristic curve.

A p value <0.05 was considered significant. Odds ratios and the confidence interval at 95% were calculated. Statistical analysis used IBM SPSS Statistics for Mackintosh, version 21.

3. RESULTS

In all, 151 patients (112 men and 39 women) were included, with a mean age of 67.4 (SD 11.9) years. Of these patients, 101 were treated with intravenous rtPA.

During this study 23 patients died (7 during admission before day 7, 11 between discharge and 6 months after stroke and 5 after that time point). One patient (0.66%) was lost for clinical and EEG follow-up in the last 6 months of the study. From the 127 alive patients with a clinical follow-up one-year after stroke, 117 (92.1%) repeated EEG by that time. Study flowchart is represented in **Figure 8.**

Demographic, clinical, imaging and electroencephalographic findings, and functional outcome are compared between patients treated and not treated with rtPA in **Table 11**. Patients undergoing alteplase were significantly older and had a higher NIHSS score at admission. After the perfusion of rtPA, the NIHSS score of treated patients was not different from that obtained at hospital admission in non-treated patients.

All (151) patients had at least one acute CT scan (1st CT). Furthermore, in the acute phase, a 2nd CT scan was performed in 129 (85.4%) patients and an MRI in 63 (41.7%) patients. Concerning imaging characteristics, in 146 patients (96.7%) the visible ischaemic lesion in the acute imaging study (1st CT scan, 2nd CT scan or MRI) was limited to the MCA territory. In 4 patients the MCA infarct was only identified by MRI. From MCA territory limited infarct patients, 124 (84.9%) performed a 2nd CT. Furthermore, in 2 patients an anterior cerebral artery (ACA) infarct was also present and 3 patients had an ACA acute lesion on CT scan study with no evidence of MCA involvement. For this reason, from the 129 patients who performed a 2nd CT scan, for 5 patients with ACA infarcts ASPECTS was not calculated. No statistically significant differences were found between CT scan features, except for a larger percentage of patients with subcortical infarcts in the group receiving rtPA.

Table 11. Clinical, imaging and neurophysiologic characteristics of patients treated and not treated with alteplase

	Patients treated with alteplase	**Patients not treated with alteplase**	p
Clinical characteristics (n=151)			
Number of patients	101	50	
Age (years)	Mean: 69.64; SD: 10.55	Mean: 62.72; SD: 13.26	**0.002**
Sex (Men/Women)	63/38 (63.4%/37.6%)	26/24 (52.0% / 48.0%)	0.223
Stroke Aetiology Cardioembolism Large-artery atherosclerosis Small-vessel occlusion Undetermined aetiology Other determined aetiology	 52 (51.5%) 25 (24.8%) 2 (2.0%) 19 (18.8%) 3 (3.0%)	 25 (50.0%) 12 (24.0%) 2 (4.0%) 10 (20%) 1 (2.0%)	 NA
NIHSS at admission	Median: 14; IQR: 9	Median: 9; IQR: 12	**0.007**
NIHSS after rtPA or at admission (for patients not treated)	Median: 12; IQR: 10	Median: 9; IQR: 12	0.262
NIHSS at discharge	Median: 8; IQR: 13	Median: 5.5; IQR: 10	0.584
NIHSS at 12 months	Median: 6.5; IQR: 11	Median: 5.5; IQR: 9	0.572

	Patients treated with alteplase	**Patients not treated with alteplase**	
Imaging Characteristics			
Territory ACA MCA	 4 (4.0%) 99 (98.0%)	 1 (2.0%) 49 (98.0%)	
Characteristics of MCA strokes in the 2nd CT scan (n=124)			
Number of patients	93	31	
Exclusively cortical	30 (32.3%)	12 (38.7%)	0.511
Exclusively subcortical	21 (22.6%)	1 (3.2%)	**0.014**
Total ASPECTS	Median: 7; IQR: 4	Median: 5; IQR: 4	0.200
Cortical ASPECTS	Median: 5; IQR: 4	Median: 4; IQR: 3	0.087
Other characteristics of the 2nd CT (n=129)			
Number of patients	97	32	
Islands of preserved cortex within the infarct	20 (20.6%)	6 (18.8%)	0.819
Haemorrhage	17 (17.5%)	6 (18.8%)	0.875
EEG Characteristics 1 (n=151)			
Number of patients	101	50	
1st EEG BA diffuse slowing	44 (43.6%)	13 (26.0%)	**0.036**
1st EEG BA asymmetry	59 (58.4%)	28 (56.0%)	0.777
1st EEG Suppression	8 (7.9%)	4 (8.0%)	1.000
1st EEG FSWA	89 (88.1%)	45 (90.0%)	0.731

	Patients treated with alteplase	**Patients not treated with alteplase**	
EEG Characteristics 2 (n=151)			
Number of patients	101	50	
1st EEG RSWA	18 (17.8%)	8 (16.0%)	0.780
1st EEG PD	11 (28.9%)	16 (14.2%)	0.381
1st EEG IEA	20 (19.8%)	7 (14.0%)	0.867
Any EEG during hospitalization with IEA and/or electrographic seizures	19 (18.8%)	8 (16.0%)	0.671
Functional outcome			
At discharge (mRS ≥ 3)	70 (69.3%)	29 (58.0%)	0.169
At 12 months (mRS ≥ 3)	58 (57.4%)	19 (38.8%)	**0.032**

Legend to table 11: ACA - anterior cerebral artery; MCA - middle cerebral artery; ASPECTS - Alberta stroke program early CT score; BA - background activity; 2nd CT scan - brain CT scan performed 24 hours after stroke; 1st EEG - EEG performed in the first 72 hours after stroke; FSWA - focal slow wave activity; IEA - interictal epileptiform activity; IQR - interquartile range; mRS - modified Rankin scale; NA - not applicable; NIHSS - National Institute of Health Stroke Scale score; PD - periodic discharges; RSWA - rhythmic slow wave activity; rtPA - intravenous alteplase; SD - standard deviation; Suppression - focal or diffuse EEG suppression; bold values - $p<0.05$

3.1. Epileptic events and Alteplase

The frequency of epileptic events can be seen in **Table 12**. Of the 101 patients undergoing rtPA, only 5 (5.0%) had paroxysmal clinical events during the perfusion of rtPA (**Appendix L**)

Table 12. Intravenous alteplase and epileptic events

	Patients treated with alteplase n=101	**Patients not treated with alteplase** n=50	p
Seizures during the study period (n=38)	25 (24.8%)	13 (26.0%)	0.868
Acute symptomatic seizures (n=22)	14 (13.9%)	8 (16.0%)	0.726
Unprovoked seizures (n=23)	16 (16.7%)	7 (14.6%)	0.748
Seizures in the first 24 hours (n=12)	6 (5.9%)	6 (12.0%)	0.213
Electrographic seizures (n=7)	6 (5.9%)	1 (2.0%)	0.426
IEA and/or electrographic seizures in any EEG during hospitalization (n=27)	19 (18.8%)	8 (16.0%)	0.671
NCSE during hospitalization (n=4)	3 (3.0%)	1 (2.0%)	1.000

Legend to table 12: IEA - interictal epileptiform activity; NCSE - nonconvulsive *status epilepticus*

3.2. EEG abnormalities and Alteplase

In the 1st EEG, diffuse slowing of the background activity was significantly more frequent in patients treated with rtPA. This difference was no longer significant at discharge nor 12 months after stroke (**Table 13).** In fact, comparing changes over time in the same group, in patients treated with rtPA a smaller proportion of records at discharge (compared to the 1st EEG) were diffusely slowed ($p<0.0005$). This difference was not observed in not treated patients ($p=0.625$).

Table 13. Intravenous alteplase and diffuse slowing of the background activity

BA diffuse slowing in the:	**Patients treated with alteplase** n=101	**Patients not treated with alteplase** n=50	p
1st EEG	44 (43.6%)	13 (26.0%)	**0.036**
Discharge EEG	23 (24.0%)	13 (19.1%)	0.517
12 months EEG	9 (11.8%)	4 (10.0%)	0.765

Legend to table 13: BA - background activity; 1st EEG - EEG performed in the first 72 hours after stroke, bold value - $p<0.05$

In a logistic regression model, 1st EEG background activity diffuse slowing was no longer predicted by rtPA when adjusted for age, NIHSS on admission and ASPECTS. The variables that remained statistically significant were age ($p=0.017$, OR 1.05, 95%CI 1.01-1.10) and ASPECTS ($p=0.001$, OR 0.73, 95%CI 0.61-0.89).

3.3. Post-stroke Seizures, Alteplase and Outcome

Age (p=0.236), admission NIHSS (p=0.605) and ASPECTS (0.886) were similar between seizure patients in rtPA treated and non-treated groups. The percentage of patients with seizures and an unfavourable outcome 12 months after stroke (n=29) was also similar (p=1.000, OR=0.95, 95%CI 0.20-4.63) between groups. Post-stroke seizures were associated with an unfavourable functional outcome, 12 months after stroke, both in rtPA treated (n=19 (76%) vs. n=6 (24%), p=0.03, OR=3.00, 95% CI: 1.08-8.35) and non-treated (n=10 (76.9%) vs. n=3 (23.1%), p=0.002, OR=10.00, 95% CI: 2.24-44.57) patients.

In a logistic regression model, unfavourable functional outcome at 12 months was no longer predicted by post-stroke seizures when adjusted for age, clinical and imaging stroke severity, both in rtPA treated (p=0.834, OR 1.15, 95%CI 0.31-4.30) and not treated patients (p=0.331, OR 3.16, 95%CI 0.310-32.27).

4. DISCUSSION

In our study, patients with an anterior circulation stroke treated with rtPA had the same frequency of acute symptomatic and unprovoked seizures, and EEG epileptic phenomena, compared to patients not submitted to thrombolysis. This observation goes against previous studies. De Reuck and Van Maele[162] in a retrospective observational study, suggest a "tendency" for patients submitted to thrombolysis to have fewer seizures (mainly unprovoked) than patients who did not receive this treatment. Vincent Alvarez and collaborators[28], in a case-control study, identified intravenous thrombolysis as an independent risk factor for early seizures. rtPA was also found to be of predictive value for electrical epileptic activity in the univariate analysis in Carrera and collaborators study[29]. Stroke severity and its cortical location are known risk factors for seizures after ischaemic stroke[25,174]. In our study, infarct clinical and imaging severity and its cortical involvement (all measured after rtPA treatment) were similar between groups, probably explaining our different results.

In our sample of patients submitted to intravenous thrombolysis, 5% had paroxysmal clinical events during rtPA perfusion, similarly to four clinical cases previously reported in the literature[30,32,33], one of which had proven cortical origin[33]. Although this observation may indicate a higher risk of cortical hypersynchronisation or epileptic phenomena in patients treated with rtPA in the first hours of ischaemic stroke, there is a possibility of detection bias, due to closer monitoring of the neurological condition in treated patients during intravenous rtPA perfusion.

Seizures after stroke have been associated with higher risks of mortality and disability[44,45,79,80,268]. This has also been observed in rare clinical studies on the effect of post-stroke seizures in functional outcome in the subgroup of patients treated with intravenous alteplase. Vincent Alvarez et al.[28] found that rtPA treated patients with post-stroke seizures (n=12) have an unfavourable functional outcome at three months. In Gensicke et al's study[172], seizures (n=37) were independent predictors of long-term poor outcome in rtPA treated patients. In our study, seizures were not associated with death or functional dependency one year after stroke, when adjusted for known outcome predictors such as age and stroke (clinical and imaging) severity, both in rtPA treated and non-treated group.

Given the higher percentage of patients with subcortical infarcts in the rtPA treated group (vs. not treated group), the presence of diffuse background slowing in this group is not totally unexpected since subcortical lesions could result in diffuse slowing as compared to focal cortical lesions (with focal slowing). Nevertheless, we have shown that age and imaging stroke severity are independently associated with slowing of background activity of the 1st EEG. In our series, rtPA patients were older and had more severe strokes at admission than non-treated patients (measured by NIHSS at admission), justifying slowing of the background activity in 1st EEG of these patients. Furthermore, discharge and 12 months after stroke NIHSS scores were similar in rtPA treated and not treated patients, possibly explaining why this EEG characteristic ceases to be a differentiating factor between rtPA treated and not treated patients at these time points.

The major strength of this prospective study is the large sample size of acute anterior circulation stroke patients with electroencephalographic evaluation and 1-year follow-up. There are potential limitations, however, including the lack of continuous EEG monitoring and universal MRI. Data supporting the benefit of continuous over spot EEG recordings to detect seizures is limited[76], especially in patients admitted in non-intensive profile departments and its cost-effectiveness is still in debate[257]. Furthermore, subtle seizures arising from small foci or deep foci for the recording electrodes, may not have surface EEG correlates and can potentially result in minor underestimation of seizure frequency.

In summary, patients treated with rtPA had the same frequency of epileptic manifestations (either clinical or electroencephalographic) as non-treated patients. Functional outcome of patients with post-stroke seizures was not different between groups.

X. PROJECT 7

"EEG may be of value in
helping the clinician estimate the risk for seizures in the post infarction patient"
Gregory Holmes (1980)

EARLY EEG PREDICTS POST-STROKE EPILEPSIA

AUTHORS

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ABSTRACT

Objective: Electroencephalography can identify biomarkers of epileptogenesis and ictogenesis. However, few studies used EEG in the prediction of post-stroke seizures. Our main aim has to evaluate whether early EEG abnormalities can predict post-stroke epilepsy.

Methods: A prospective study of consecutive anterior circulation ischaemic stroke patients, without previous epileptic seizures, admitted to a Stroke Unit over 24 months and followed-up for one year. All patients underwent standardized clinical and diagnostic assessment during hospitalization and after discharge. Video-EEG was performed in the first 72 hours (1st EEG), daily for the first 7 days, in case of neurological deterioration, at discharge and at 12 months after stroke. The occurrence of epileptic seizures in the 1st year after stroke was clinically and neurophysiologically evaluated during hospitalization and at 12 months. A telephone interview was also performed at 6 months. Primary outcome was the occurrence of at least one unprovoked seizure (post-stroke epilepsy). Secondary outcomes were the occurrence of at least one acute symptomatic seizure and (interictal and/or ictal) epileptiform activity on at least one EEG during the hospital stay for acute stroke. 1st EEG variables were defined using international criteria/terminology. Bivariate and multivariate analyses with adjustment for age, admission NIHSS and ASPECTS were performed.

Results: 151 patients were included. 38 (25.2%) patients had at least one epileptic seizure and 23 (16%) an unprovoked seizure. First EEG background activity asymmetry and 1st EEG with interictal epileptiform activity were independent predictors of post-stroke epilepsy during the first year after stroke. (p=0.043 and p=0.043, respectively). No EEG abnormality independently predicted acute symptomatic seizures. However, the presence of periodic discharges in the 1st EEG was an independent predictor of epileptiform activity (p=0.009) during hospital stay.

Significance: An early post-stroke EEG can predict epilepsy in the first year after stroke, independently from clinical and imaging-based infarct severity.

KEY-WORDS

ischaemic stroke, epileptic seizures, prediction, EEG

1. INTRODUCTION

Clinical stroke severity and infarct dimension are known risk factors for post-stroke epileptic seizures and vascular epilepsy[27]. Although EEG is a sensitive neurophysiological technique in the detection of acute cerebral ischaemia[36] and a robust one in the functional assessment of the brain[37], it is unclear whether electroencephalographic markers of acute vascular injury severity are independently associated with an increased risk of post-stroke seizures or useful for their prediction. A single retrospective study[51] showed an association between diffuse EEG background slowing in acute stroke phase and seizure occurrence. Furthermore, even though the presence of periodic discharges and frontal intermittent rhythmic delta activity have been associated with the occurrence of acute symptomatic seizures[51], it is still unknown whether electroencephalographic markers of cortical hypersynchronisation and of an epileptogenic zone may be helpful in the prediction of unprovoked seizures or post-stroke epilepsy, according to the current definition[93].

Our primary aim was to investigate whether early EEG abnormalities are independent predictors of post-stroke epilepsy.

2. METHODS

Ours was a prospective study of consecutive patients with an acute anterior circulation ischaemic stroke, admitted to the Stroke Unit of a Neurology Department between October 2011 and October 2013 and followed-up for 12 months. The Ethics Committee "Comissão de Ética para a Saúde" of the HSM-CHLN approved this study.

The following inclusion criteria were used:

(1) Acute anterior circulation ischaemic stroke, established by imaging (CT scan or MRI), with less than 7 days of clinical evolution

(2) National Institutes of Health Stroke Scale (NIHSS) score ≥ 4 upon admission to the emergency department

(3) Signed informed consent by the patients or their next-of-kin

The subsequent exclusion criteria were used:

(1) Posterior circulation vascular syndrome[269] even if not confirmed by imaging

(2) Acute posterior circulation ischaemic stroke, established by imaging (CT scan or MRI) obtained at any time during hospitalization

(3) Previous stroke with modified Rankin scale score (mRS)[236] > 1 at the time of acute stroke

(4) Brain imaging study (any CT scan or MRI) with one of the following: contusion; subdural/epidural hematoma; subarachnoid haemorrhage; neoplastic lesion; infectious/inflammatory lesion; hydrocephalus

(5) Brain CT scan performed in the emergency department (1st CT Scan) with intracerebral haemorrhage

(6) Previous history of head trauma with hospital admission

(7) Previous neurosurgery

(8) Previous history of epilepsy or epileptic seizures

2.1. Standardized clinical and ancillary evaluation

All patients were attended by a neurologist at the emergency department and admitted to our Stroke Unit with continuous surveillance of their neurological status and daily observation by a stroke neurologist. During the study period, this Stroke Unit admitted all patients treated with intravenous alteplase (rtPA) in our hospital (according to ESO Guidelines[72]) and, depending on bed availability, also patients not treated with rtPA. The NIHSS score and seizure occurrence were prospectively recorded. During hospitalization, the patient performed diagnostic tests allowing stroke etiological classification[239] and appropriate therapeutic approach, including blood tests, carotid and vertebral duplex scans, transcranial Doppler and ECG. All patients underwent a CT scan at the emergency department (1st CT scan) which was repeated 24 hours after stroke in patients submitted to rtPA and when clinically indicated in all patients (2nd CT scan). Selected patients also performed MRI with diffusion weighted imaging, transthoracic or transesophageal echocardiography, 24h Holter or cerebral angiography.

After discharge patients had a standard clinical follow-up at the cerebrovascular outpatient clinic. A neurologist with expertise in epilepsy (CB) performed a telephone interview 6 months after stroke accessing seizure occurrence by a free interview followed by a brief phone screening tool for identifying patients with epilepsy[240]. A scheduled appointment 12 months after stroke was also conducted (CB), recording the following clinical variables: NIHSS and mRS score, occurrence of seizures and type; other stroke or medical complications; final etiological classification of stroke[239] and ongoing therapy.

2.2. Neurophysiological Evaluation

All patients underwent a neurophysiological evaluation protocol[270] that included a 64 channel synchronized video-EEG with a maximum duration of 60 minutes in different time frames after stroke:

(1) As early as possible, in the first 72 hours after admission (1st EEG)

(2) Daily, after the 1st EEG, for the first 7 days after stroke (except on weekend)

(3) If neurological worsening, unexplained by medical complications, and with indication for repeating the imaging exam

(4) At time of clinical discharge (discharge EEG)

(5) At 12 months after stroke (12M EEG)

2.3. Imaging Interpretation

All imaging exams performed during the study period were reviewed by 2 senior neuroradiologists (CM and CC), blinded for clinical and electroencephalographic findings and trained for ASPECTS classification. Doubts were discussed and final determination was reached by consensus.

In patients with an infarct limited to the middle cerebral artery (MCA) territory in the imaging study (considering 1st CT scan, 2nd CT scan or MRI), the infarct size was quantified by ASPECTS[42] in 1st and 2nd CT scan. Insula and M1 to M6 ASPECTS territories were considered "cortical territories of ASPECTS". Furthermore, any type of haemorrhage transformation[242], cortical or subcortical infarct location, presence of cortical areas with normal attenuation coefficient (islands of preserved cortex) within the infarct[165,243,244] were evaluated in 2nd CT.

2.4. Outcomes

The primary outcome of this study was the occurrence of at least one unprovoked epileptic seizure (post-stroke epilepsy[44,93]), one year after stroke.

The secondary outcomes were the occurrence of: at least one acute symptomatic seizure and EEG epileptiform activity in at least one EEG during hospitalization

The following operational definitions were used:

(1) Unprovoked seizures (or post-stroke epilepsy[44,93]): at least one clinical seizure[93] occurring 7 days after (and in the first year of) a stroke, in the absence of precipitating factors[142]

(2) Acute symptomatic seizure: at least one epileptic seizure occurring within the first 7 days of a stroke [142]. In these patients, cut-off values for metabolic disorders and febrile symptomatic seizures were not overreached and alcohol/drug withdrawal or intoxication[142] were excluded

(3) Electrographic seizure; generalized spike-wave discharges at 3/s or faster or clearly evolving discharges of any type that reach a frequency >4/s, whether focal or generalized[212]. Evolving was defined as at least 2 unequivocal sequential changes in frequency, morphology or location lasting for at least 3 cycles each. Evolution in frequency was defined as at least 2 consecutive changes in the same direction by at least 0.5/s. Evolution in morphology was defined as at least 2 consecutive changes to a novel

morphology. Evolution in location was defined as sequentially spreading into or sequentially out of at least two different standard 10-20 electrode locations and persisting for least 3 cycles[212]

(4) EEG epileptiform activity during hospitalization (interictal or ictal): At least one EEG during hospitalization with interictal epileptiform activity (IEA) [211] and/or an electrographic seizure [212]

2.5. Predictors

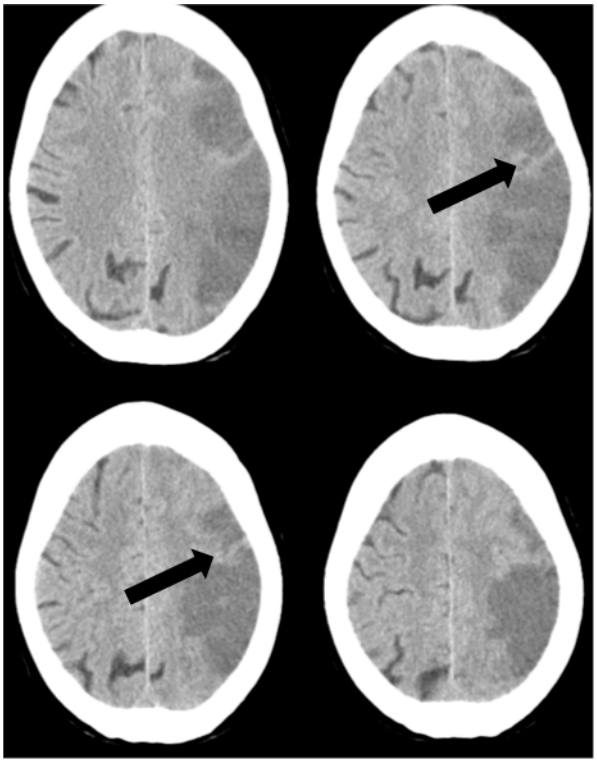
The following characteristics were studied:

(1) Clinical characteristics: age, admission NIHSS[70] and TOAST subgroups[239]

(2) Imaging characteristics: 1st CT ASPECTS [42] (and cortical territories of ASPECTS), 2nd CT with islands of preserved cortex within the infarct[165,243,244] (**Figure 12**) and any intracerebral haemorrhage[242].

(3) 1st EEG abnormalities: background activity slowing[211]; asymmetry[212]; suppression (focal, hemispheric or diffuse)[212]; Focal Slow Wave Activity[211] (FSWA), defined as continuous or intermittent slow activity i.e. theta and/or delta band activity, without an approximately constant period, limited to an area of the brain or scalp region (including focal and regional concept of the International Federation of Clinical Neurophysiology[211]; rhythmic slow wave activity (RSWA), including lateralized rhythmic delta activity (LRDA) definition by ACNS[212] and rhythmic delta/theta (>0.5 Hz) activity[245], interictal epileptiform activity (IEA)[211]; periodic discharges (PD)[212]; electrographic seizure[212].

Figure 12. Islands of preserved cortex within the infarct



Legend to figure 12: Brain CT- scan showing an acute left middle cerebral artery ischaemic stroke. Black arrows indicate cortical areas with normal attenuation coefficient (islands of preserved cortex) within the infarct.

2.6. Statistical analysis

A descriptive analysis was used for nominal qualitative and quantitative variables. Nominal variables are expressed in frequency, discrete variables as medians and interquartile ranges (IQR) and continuous variables as means and standard deviations (SD).

The bivariate analysis of qualitative variables was performed by χ^2 test, Fisher exact test or McNemar test and of quantitative variables by t-student or Mann-Whitney U tests, as appropriate.

Variables with a significant association in bivariate analysis were adjusted in a logistic regression model for known functional outcome predictors of stroke and post-stroke seizures [27,39–42], namely age, clinical stroke severity (admission NIHSS) and imaging infarct size

(ASPECTS), when meeting the requirements for this analysis. The significance level was $\alpha<0.05$. The odds ratios (OR) and the confidence interval of 95% were calculated.

Defined characteristics of outcome prediction models encompassing predictors with the highest odds to impact outcome were studied. The percentage of patients correctly identified by the models was calculated. Model calibration was analysed by Hosmer-Lemeshow test and discriminative capacity measured by the area under the ROC curve. In all models, the study of the assumptions associated with logistic regression showed the existence of a multicollinearity problem between the variables “ASPECTS” and “cortical territories of ASPECTS”. Only the first was included in the logistic regression models.

Statistical analysis was done using SPSS program version 24 for Mac.

3. RESULTS

A total of 151 patients (112 men) with a mean age of 67.4 (SD 11.9) years was included. The study flowchart was previously described [271] (**Figure 8**) . Median NIHSS was 12 (IQR 10) at admission.

An infarct limited to middle cerebral artery territory (MCA) was observed in 146 (96.7%) patients and to anterior cerebral artery territory (ACA) in 3 (2.0%) patients. Two patients had simultaneously MCA and ACA infarcts. Patients with an exclusively MCA infarct had a median 1st CT ASPECTS of 9 (IQR 3), scoring 6 (IQR 3) in the cortical territories of this scale.

All patients performed at least one EEG during hospitalization in a median time of 1 day (IQR 1) after stroke (1st EEG). The median number of records performed per patient was 5 (IQR 3).
Seven patients died during hospitalization. Of the 144 discharged patients, 143 patients (99.3%) performed an EEG on this date. One patient (0.7%) refused to undergo this exam. The discharge EEG was made on a median time of 7 days after stroke.
Of the 127 patients who were alive at 12 months, 117 (92.1%) performed an EEG at this time and 10 patients (7.9%) refused to repeat the exam. One patient (0.66%) was lost to clinical and neurophysiological follow-up between month 6 and 12.

The frequency of EEG abnormalities is described in **Table 14**. Clinical and imaging characteristics associated with early EEG abnormalities are described in **Appendix M**. In the first 7 days after stroke, 7 patients had at least one electrographic seizure (5 of which had exclusively electrographic seizures and 2 patients both clinical and electrographic seizures). Clinical, imaging characteristics and EEG abnormalities associated with these events are disclosed in **Appendix N**.

During the study period, 38 (25.2%) patients had at least one epileptic seizure, 22 (14.6%) an acute symptomatic seizure and 23 (16%) an unprovoked seizure. Furthermore, 5 patients had pure electrographic seizures during hospital stay.

Table 14. EEG abnormalities in different time frames after stroke

	1st EEG [a] n (%)	**Serial EEG** n (%)	**Mc.Nemar´s test 1**[c] p	**Discharge EEG**[d] n (%)	**Mc.Nemar´s test 2**[e] p	**12M EEG** [f] n (%)	**Mc.Nemar's test 3**[g] p
n	151	151	-	143	-	116	-
BA[h] **slowing**	57 (37.7%)	57 (37.7%)	ns[m]	32 (22.4%)	<0.0005	13 (11.2%)	<0.0005
BA asymmetry	64 (42.4%)	44 (29.1%)	<0.0005	42 (29.4%)	<0.0005	20 (17.2%)	<0.0005
Suppression	12 (7.9%)	19 (12.6%)	0.016	10 (7%)	ns	1 (0.9%)	ns
FSWA[i]	134 (88.7%)	143 (94.7%)	0.004	124 (86.7%)	ns	99 (85.3%)	ns
RSWA[j]	26 (17.2%)	38 (25.2%)	<0.0005	17 (11.9%)	ns	9 (7.8%)	0.031
PD[k]	27 (17.9%)	38 (25.2%)	0.007	9 (6.3%)	0.002	3 (2.6%)	0.002
IEA[l]	16 (10.6%)	18 (11.9%)	ns	12 (8.4%)	ns	5 (4.3%)	ns
Electrographic seizures[m]	1 (0.7%)	6 (4.0%)	ns	0	ns	0	ns

Legend to table 14: [a]1st EEG - video-EEG performed in the first 72 hours after admission; [b]Serial EEG - video-EEG performed daily for the first 7 days after stroke (except on weekend) or if neurological worsening unexplained by medical complications and with indication for repeating the imaging exam (at least one EEG record during the hospitalization with one of the analysed features); [c]Mc. Nemar´s test 1 - Mc. Nemar´s test defining the difference between 1st EEG and serial EEG; [d]Discharge EEG - video-EEG performed at time of clinical discharge; [e]Mc. Nemar´s test 2 - Mc. Nemar´s test defining the difference between 1st EEG and discharge EEG; [f]12M EEG - video-EEG performed at 12 months after stroke; [g]Mc.Nemar´s test 3 - Mc. Nemar´s test defining the difference between 1st EEG and 12 months EEG; [h]BA – background activity; [i]FSWA - focal slow wave activity; [J]RSWA - rhythmic slow wave activity; [k]PD - lateralized periodic discharges; [l]IEA - interictal epileptiform activity; [m]ns - non-significant ($p > 0.05$)

3.1. Defined outcome predictors

Clinical, imaging and 1st EEG variables associated with defined outcomes are disclosed in **Table 15 to 16** and **Appendix O**.

3.1.1. 1st EEG independent predictors of defined outcomes

1st EEG background activity asymmetry was an independent predictor of unprovoked seizures during the first year after stroke. The occurrence of interictal epileptiform activity in the 1st EEG was also an independent predictor of unprovoked seizures. No EEG abnormality independently predicted acute symptomatic seizures. However, the presence of periodic discharges in the 1st EEG was an independent predictor of epileptiform activity (interictal and/or ictal) in at least one EEG during the hospital stay. No other studied 1st EEG abnormality was an independent predictor of defined outcomes.

3.1.2. Imaging independent predictors of defined outcomes

ASPECTS was an independent predictor of unprovoked seizures and also acute symptomatic seizures. The presence of islands of preserved cortex within the infarct was an independent predictor of the presence of interictal epileptiform activity and/or electrographic seizures in at least one EEG during the hospital stay.

3.1.3. Other independent predictors of defined outcomes

Unprovoked seizures were also independently associated with the occurrence of a previous acute symptomatic seizure.

Table 17 displays the characteristics of prediction models for defined outcomes. All models have a good to very good discriminative capacity.

Table 15. Clinical, imaging and neurophysiological predictors of unprovoked seizures (post-stroke epilepsy)

Unprovoked seizures	**Yes**	**No**	**Bivariate analysis**[o] p OR[a]; 95% CI[b]	**Multivariate analysis**[p] p OR; 95% CI
Demographic and clinical characteristics of patients with > than 7 days of follow-up (n=144)				
Number of patients	23	121		
Mean Age (SD[c])	64.9 (13.3)	67.5 (11.3)	0.466	NA
Median admission NIHSS[d] (IQR[e])	16 (7)	11 (10)	**0.009**	0.146 1.07; 0.98-1.16
Stroke aetiology: Cardio embolism	14 (60.9%)	62 (51.2%)		
Atherosclerosis	5 (21.7%)	31 (25.6%)		
Small vessels	1 (4.3%)	3 (2.5%)	0.156	NA
Undetermined	1 (4.3%)	23 (19.0%)		
Other	2 (8.7%)	2 (1.7%)		
Previous acute symptomatic seizure	7 (30.4%)	9 (7.4%)	**0.001** 5.44**;** 1.78-16.65	**0.019** 4.47**;** 1.28-15.68

Unprovoked seizures	**Yes**	**No**	**Bivariate analysis**[o] p OR[a]; 95% CI[b]	**Multivariate analysis**[p] p OR; 95% CI
Imaging stroke characteristics				
Isolated MCA[f] **territory infarct patients with > than 7 days of follow-up** (n=140)				
Number of patients	21	119		
1st CT median ASPECTS[h] (IQR)	8 (3)	9 (1)	**0.002**	**0.020** 0.73**;** 0.56-0.95
1st CT median CORTICAL[i] ASPECTS (IQR)	5 (3)	6 (2)	**0.002**	**0.020** 0.73; 0.56-0.95
Isolated MCA infarct patients with a 2nd CT[j] **and > than 7 days of follow-up** (n=119)				
Anterior circulation ischaemic stroke patients with a 2nd CT scan and > than 7 days of follow-up (n=123)				
Number of patients	23	100		
Islands of preserved cortex within the infarct	8 (34.8%)	17 (17.0%)	0.056 2.60; 0.95-7.11	NA
Haemorrhage	6 (26.1%)	16 (16.0%)	0.255 1.85; 0.63-5.42	NA

Unprovoked seizures	**Yes**	**No**	**Bivariate analysis**[o] p OR[a]; 95% CI[b]	**Multivariate analysis**[p] p OR; 95% CI
1st EEG characteristics (n=151)				
Number of patients	23	121		
BA[j] diffuse slowing	12 (52.2%)	38 (31.4%)	0.055 2.38; 0.96-5.88	NA
BA asymmetry	16 (69.6%)	43 (35.5%)	**0.002** **4.15; 1.58-10.87**	**0.043** 3.16; 1.04-9.65
Suppression	4 (17.4%)	4 (3.3%)	**0.023** **6.16; 1.42-26.74**	NA
FSWA[k]	22 (95.7%)	106 (87.6%)	0.469 3.11; 0.39-24.81	NA
RWSA[l]	8 (34.8%)	16 (13.2%)	**0.011** **3.50; 1.28-9.58**	0.062 2.92; 0.95-8.97
PD[m]	7 (30.4%)	18 (14.9%)	0.071 2.50; 0.90-6.94	0.424 1.61; 0.50-5.16
IEA[n]	7 (30.4%)	8 (6.6%)	**0.001** **6.18, 1.97-19.35**	**0.043** 3.84; 1.04-14.13

Legend to table 15: [a]OR - odds ratio; [b]CI - confidence interval; [c]SD - standard deviation; [d]NIHSS - National Institutes of Health Stroke Scale score; [e]IQR - interquartile range; [f]MCA - middle cerebral artery; [g]1st CT - 1st CT scan obtain at the emergency department; [h]ASPECTS - Alberta Stroke Program Early CT Score; [i]Cortical ASPECTS - value in ASPECTS considering only the 7 cortical territories of this scale; [j]BA - background activity; [k]FSWA - focal slow wave activity; [l]RSWA - rhythmic slow wave activity; [m]PD - periodic discharges; [n]IEA - interictal epileptiform activity; [o]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate. Bold values - $p<0.05$; [p]Multivariate analysis - variables with a positive significant association in bivariate analysis, were adjusted for age, admission NIHSS and ASPECTS, using a logistic regression model. The OR for age, NIHSS, and ASPECTS are derived from multivariable logistic models including exclusively these three variables, whereas the OR for the EEG variables are derived from models including age, NIHSS, ASPECTS and the respective EEG variable. Bold values - $p<0.05$

Table 16. Clinical, imaging and neurophysiological predictors of EEG epileptiform activity during hospital stay

IEA and/or electrographic seizures during hospitalization	**Yes**	**No**	**Bivariate analysis**[o] p OR; 95% CI	**Multivariate analysis**[p] p OR; 95% CI
Demographic and clinical characteristics (n=151)				
Number of patients	27	124		
Mean Age (SD)	70.8 (12.1)	66.6 (12.1)	0.076	NA
Median admission NIHSS (IQR)	15 (15)	12 (10)	**0.019**	0.214 1.05; 0.97-1.13
Stroke aetiology: Cardio embolism	18 (66.7%)	59 (47.6%)		
Atherosclerosis	5 (18.5%)	32 (25.8%)		
Small vessels	0 (0%)	4 (3.2%)	0,388	NA
Undetermined	4 (14.8%)	25 (20.2%)		
Other	0 (0%)	4 (3.2%)		

IEA and/or electrographic seizures during hospitalization	**Yes**	**No**	**Bivariate analysis**[o] p OR; 95% CI	**Multivariate analysis**[p] p OR; 95% CI
Imaging stroke characteristics				
Isolated MCA[d] **territory infarct** (n=146)				
Number of patients	25	121		
1st CT[g] median ASPECTS[h] (IQR)	9 (3)	9 (2)	**0.029**	0.105 0.82; 0.640-1.043
1st CT median CORTICAL[i] ASPECTS (IQR)	6 (3)	6 (2)	**0.029**	0.105 0.82; 0.640-1.043
Anterior circulation ischaemic stroke patients with a 2nd CT scan (n=129)				
Number of patients	25	104		
Islands of preserved cortex within the infarct	11 (44.0%)	15 (14.4%)	**0.001** **4.66; 1.78-12.1**	**0.01** **4.29; 1.41-13.1**
Haemorrhage	6 (24.0%)	17 (16.3%)	0.369	NA

1st EEG characteristics (n=151)				
Number of patients	27	124		
BA[j] diffuse slowing	13 (48.1%)	44 (35.5%)	0.219 1.69; 0.73-3.91	NA
BA asymmetry	18 (66.7%)	46 (37.1%)	**0.005** **3.39; 1.41-8.20**	0.055, 2.64, 0.98-7.14
Suppression	3 (11.1%)	9 (7.3%)	0.450 1.60; 0.40-6.34	NA
FSWA[k]	26 (96.3%)	108 (87.1%)	0.311 3.85; 0.49-30.38	NA
RWSA[l]	7 (25.9%)	19 (15.3%)	0.186 1.93; 0.72-5.20	NA
PD[m]	12 (44.4%)	15 (12.1%)	**<0.0005** **5.81; 2.29-14.76**	**0.009** **3.88, 1.41-10.70**
IEA[n]	16 (59.3%)	0 (0%)	**NA**	NA

Legend to table 16: [a]OR - odds ratio; [b]CI - confidence interval; [c]SD - standard deviation; [d]NIHSS - National Institutes of Health Stroke Scale score; [e]IQR - Interquartile range; [f]MCA - middle cerebral artery; [g]1st CT - 1st CT scan obtain at the emergency department; [h]ASPECTS - Alberta Stroke Program Early CT Score; [i] Cortical ASPECTS - Score in ASPECTS considering only the 7 cortical territories of this scale; [j]BA - background activity ; [k]FSWA - focal slow wave activity; [l]RSWA - rhythmic slow wave activity; [m]PD - periodic discharges; [n]IEA - interictal epileptiform activity; [o]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate; [p]Multivariate analysis - variables with a positive significant association in bivariate analysis, were adjusted for age, clinical stroke severity (admission NIHSS) and imaging infarct severity (ASPECTS), using a logistic regression model. The OR for age, NIHSS, and ASPECTS are derived from multivariable logistic models including exclusively these three variables, whereas the OR for the EEG variables are derived from models including age, NIHSS, ASPECTS and the respective EEG variable. Bold values – $p<0.05$

Table 17. Post-stroke defined outcomes binary logistic regression models' characteristics

Model Features	Omnibus Test	Nagelkerke's R^2	Hosmer & Lemeshow Test	PAC[a]	SEN[b]	SPE[c]	PPV[d]	NPV[e]	AUC[f] 95%CI[g]
Post-stroke unprovoked seizures (post-stroke epilepsy)									
Independent variables: "previous post-stroke acute symptomatic seizures" + "1st CT ASPECTS" + 1st EEG background activity asymmetry + 1st EEG with interictal epileptiform activity									
Model characteristics	$\chi^2(4)=22.58$; $p<0.0005$	26,1%	$\chi^2(6)=5.11$; $p=0.53$	85.7%	23.8%	96.6%	55.6%	87.8%	0.81 0.71-0.90
Post-stroke acute symptomatic seizures									
Independent variables: "1st CT ASPECTS"									
Model characteristics	$\chi^2(1)=6.50$ $p=0.013$	7.9%	$\chi^2(3)=0.23$; $p=0.830$	86.3%	0%	100%	0%	100%	0.72 0.63-0.82
EEG epileptiform (interictal and/or ictal) activity during hospitalization									
Independent variables: "Islands of preserved cortex within the infarct" + "1st EEG with periodic discharges"									
Model characteristics	$\chi^2(2)=19.49$ $p<0.0005$	22.4%	$\chi^2(2)=0.99$; $p=0.609$	84.5%	28.0%	98.1%	77.8%	85.0%	0.72 0.60-0.85

Legend to table 17: [a]PAC - percentage of accuracy in classification; [b]SEN - Sensibility; [c]SPE - specificity; [d]PPV - positive predictive value; [e]NPV - negative predictive value; [f]AUC - area under the ROC curve; [g]CI - confidence interval; [h]ASPECTS - Alberta Stroke Program Early CT Score

4. DISCUSSION

In this work, post-stroke epilepsy could be predicted by EEG findings, extracted from visual analysis of an early and short duration EEG, independently from clinical and imaging–based infarct severity. Indeed, for the same age, clinical and imaging infarct severity, the risk of post-stroke unprovoked seizures was 3.2 times higher in patients with 1st EEG background activity asymmetry and 3.8 times higher if interictal epileptiform activity was displayed in this exam. Furthermore, we found early neurophysiological markers of an increased risk of EEG epileptiform activity during hospital stay, identifying patients who might benefit from an extended neurophysiological study. A previous analysis of our group[270] already showed that the frequency of post-stroke seizures is clinically underestimated without a systematic neurophysiological evaluation. The present study further enlarges the importance of EEG in stroke patients defining those with an increased risk for epilepsy and also for paroxysmal EEG events during hospital stay.

Strengths of this work include the sample size with prospective clinical assessment and rigorous electroencephalographic acute evaluation and follow-up. Furthermore, this work includes standardized imaging evaluation of MCA infarct dimension and the presence of islands of preserved cortex within the infarct. Another aspect that stands out is the use of internationally recognized terminology[212] showing good inter-observer agreement[248] for describing the electroencephalographic features. The consideration of clinical and imaging parameters in the statistic models is also very pertinent.

In this study, the non-continuous nature of the neurophysiological assessment may be considered a limitation. However, we identified early neurophysiological and imaging markers that can guide the need for a more prolonged study (serial or even continuous) only in some patients, presumably improving the cost-benefit of such a procedure. Continuous EEG requires large quantities of time, specialized human resources (physicians and technicians) and is not accessible at all centres. In accordance, studies about the performance of a short duration EEG for epileptiform activity detection are important. In fact, the search for EEG markers suggesting the need and helping to identify patients for a more prolonged or frequent record, as analysed in this paper, is a current trend in electroencephalography research[255,256,272,273]. Furthermore, anti-epileptic drug prescription was not analysed in this study. Although (theoretically) anti-epileptic drug treatment could impact outcome

measures, primary and secondary prophylaxis of an index acute symptomatic seizure is not routinely performed in our Stroke Unit, in accordance to the recently published ESO guidelines[148]. Furthermore, even when repeated acute symptomatic seizures occur during hospitalization leading to antiepileptic drug prescription, their withdrawal after the acute stroke phase is encouraged. Therefore, the occurrence of unprovoked seizures one year after stroke is probably not greatly affected by anti-epileptic drug prescription in our study.

In the present work, unprovoked seizures or epilepsy (according to the current ILAE definition[93]) in the year following an anterior circulation ischaemic stroke were independently predicted by 1st EEG asymmetry (reflecting asymmetrical cerebral dysfunction) even when adjusted for age, admission NIHSS and ASPECTS. This data adds a neurophysiological risk factor to post-stroke seizures, reflecting not only their association with large and disabling ischaemic strokes[2] but also the importance of EEG for brain functional assessment. In fact, recently 1st EEG asymmetry was also reported as an independent predictor of unfavourable stroke functional outcome even when adjusted for age, clinical and imaging stroke severity[274].

Furthermore, post-stroke epilepsy was also independently predicted by the presence of interictal epileptiform activity in the 1st EEG. This observation seems physiopathologically coherent, since spikes and sharp waves are neurophysiological markers of epileptogenesis[4] and therefore of an increased susceptibility for seizures. This result is also of great clinical relevance, helping to identify patients with an increased risk of post-stroke epilepsy.

There is currently no high quality evidence providing strong support for the primary prophylactic use of anti-epileptic drugs for post-ischaemic stroke unprovoked seizures[148]. However, we think that our EEG findings can, at least, lead to stricter clinical monitoring, oriented towards an early recognition of seizures in these higher risk patients and may help earlier identification, prevention of associated risks and timely prescription of appropriate secondary prophylaxis of post-stroke unprovoked seizures. On the other hand, one should note that the European Stroke Organization “weak recommendation” against primary prophylaxis of unprovoked seizures is based on their low risk of occurrence in most stroke patients (approximately 10%)[148]. While lacking external validation, our model might help to consider the need for anti-epileptic drugs when EEG and other independent predictors of post-stroke epilepsy are present, that is, whenever the estimated risk of an unprovoked

seizure occurrence is at least similar to its recurrence risk[148], i.e. higher than 60% (95% CI = 59.7–81.9%)[44].

In our study, 1st EEG periodic discharges were an independent predictor of epileptiform activity (interictal and/or ictal) during hospitalization, reinforcing the concept that periodic discharges are in the continuum between an interictal and ictal phenomenon[250] and in accordance with the association of this neurophysiological feature to clinical and EEG epileptiform manifestations both in studies using short duration[51,165,275] and continuous EEG[75,255,256]. Another independent predictor of epileptiform activity in our study was the presence of islands of preserved cortex within the infarct. Although suggested by two case-control studies from the 90s[165,243], this association has not yet been prospectively associated with EEG epileptiform activity during hospitalization for acute stroke. It has been postulated that this finding reflects regional cerebral blood flow reduction, although at a threshold higher than that of ischaemia[243], providing a state of neuronal hyperexcitability to these regions. Peri-infarct depolarisations have been observed in stroke animal models[276] and PET studies have shown that most patients with unprovoked seizures have hypermetabolism in the infarct boundaries[277]. In addition, a recent study[278] demonstrated that interictal epileptiform activity is associated with several separated cortical microinjuries postulating that its presence may interrupt the connectivity between deep and superficial cortical layers and induce hypersynchronisation of the latter.

XI. PROJECT 8

"While the overall risk of stroke has declined by 25% in the last decade, disability from stroke is now emerging as a major public health problem, particularly in the elderly, as we observe an increase in aging of the population"

Rachel Dreyer (2014)

SEIZURES, EEG ABNORMALITIES AND OUTCOME OF ISCHAEMIC STROKE PATIENTS

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ABSTRACT

Objective: Seizures and electroencephalographic (EEG) abnormalities have been associated with an unfavourable stroke functional outcome. However, this association may depend on clinical and imaging stroke severity. We aim to analyse whether epileptic seizures and early EEG abnormalities are predictors of stroke outcome after adjustment for age and clinical / imaging infarct severity.

Methods: A prospective study was made on consecutive and previously independent acute stroke patients with a National Institutes of Health Stroke Scale (NIHSS) score ≥4 on admission and an acute anterior circulation ischaemic lesion in brain imaging. All patients underwent standardized clinical and diagnostic assessment during admission and after discharge, and were followed for 12 months. Video-EEG (<60 minutes) was performed in the first 72h. The Alberta Stroke Program Early CT Score quantified middle cerebral artery infarct size. The outcomes in this study were an unfavourable functional outcome (modified Rankin Scale [mRS] ≥3) and death (mRS=6) at discharge and 12 months after stroke.

Results: Unfavourable outcome at discharge was independently associated with NIHSS score (p=0.001), EEG background activity slowing (p<0.001) and asymmetry (p<0.001). Unfavourable outcome one year after stroke was independently associated with age (p=0.001), NIHSS score (p<0.001), unprovoked seizures (p=0.046), EEG background activity slowing (p<0.001) and asymmetry (p<0.001). Death in the first year after stroke was independently associated with age (p=0.028), NIHSS score (p=0.001), acute symptomatic seizures (p=0.015) and EEG suppression (p=0.019).

Significance: Acute symptomatic seizures were independent predictors of vital outcome and unprovoked seizures of functional outcome, in the first year after stroke. Therefore, their recognition and prevention strategies may be clinically relevant. Early

electroencephalographic abnormalities were independent predictors and comparable to age and early clinical / imaging infarct severity in stroke functional outcome discrimination, reflecting the concept that EEG is a sensitive and robust method in the functional assessment of the brain.

KEY-WORDS

seizures, epilepsy, EEG, stroke, outcome, ASPECTS

1. INTRODUCTION

Post-stroke epileptic phenomena (seizures and *status epilepticus*)[44,45,79–82] have been associated with ischaemic stroke unfavourable outcome. However, while EEG is essential for the detection of interictal and ictal epileptiform activity it is unknown whether these EEG activities *per se* are also associated with stroke prognosis.

Previous work, mainly retrospective and without standardized imaging analysis, showed that raw EEG abnormalities (other than epileptiform discharges) are associated with post-stroke functional outcome, essentially in the short-term[64,85–88]. Additionally, a few small sample studies using quantitative EEG indexes showed that these might be better than a clinical scale in functional outcome prediction[89] or have a higher correlation with the residual neurological deficit after stroke, than acute magnetic resonance imaging (MRI) lesion[71].

However, it is unknown whether the association between seizures or EEG abnormalities and stroke functional outcome is independent from known cerebral infarct outcome predictors, namely age and stroke (clinical and imaging) severity [39–42]. Thus, we aimed to prospectively assess whether seizures and post-stroke EEG abnormalities are outcome predictors at discharge and 12 months after stroke after adjustment for age and stroke severity.

2. METHODS

2.1. Study design

We performed a prospective longitudinal study of consecutive anterior circulation ischaemic stroke patients admitted to the Stroke Unit of the Neurology Department of a University Hospital over a period of 24 months and followed for 12 months. The Ethics Committee "Comissão de Ética para a Saúde" at our hospital approved this study. All subjects or their next of kin gave written informed consent for participation.

All included patients had to be previously independent (modified Rankin Scale [mRS] ≤1), score a value of at least 4 on National Institutes of Health Stroke Scale (NIHSS)[70] upon admission to the emergency department (ED), had an acute ischaemic brain lesion (noncontrast computed tomography [CT] scan or MRI) in the internal carotid artery territory and no previous history of epileptic seizures, traumatic head injury requiring hospital admission, or brain surgery.

2.2. Clinical assessment

All patients received standardized clinical and diagnostic assessment, during hospitalization and after discharge. An investigator blinded to the neurophysiological evaluation conducted a phone interview at six months and a clinical appointment 12 months after stroke to access the occurrence of epileptic seizures and functional outcome.

NIHSS score at admission assessed clinical stroke severity. The functional outcome at discharge and at 12 months was assessed by the mRS[236].

2.3. Neurophysiological evaluation

Patients underwent a neurophysiological evaluation protocol that included a 64-channel video-EEG with a maximum duration of 60 minutes in the first 72 hours after stroke (EEG). The record included an eyes closed wake resting condition and eyes open, hyperventilation and photic stimulation manoeuvers. EEG review and classification were performed by a certified clinical neurophysiologist (CB) using international criteria and terminology[211,212,245], blinded for clinical and imaging findings. All doubts were decided by consensus with another clinical neurophysiologist (ARP).

2.4. Neuroimaging interpretation

A senior neuroradiologist, (CM or CC) blinded for clinical and electroencephalographic findings analysed all the neuroimaging studies performed during hospitalization. Doubts were decided by consensus. In patients with an isolated middle cerebral artery (MCA) stroke in the imaging study (considering non-contrast-enhanced CT scan or MRI), the infarct size was quantified in the 1st CT performed after stroke by the Alberta Stroke Program Early CT Score (ASPECTS)[42]. Whenever there was a brain CT scan performed at least 24 hours after stroke onset (2nd CT scan) ASPECTS was also quantified in this exam in patients with an isolated MCA infarct.

2.5. Predictors and Outcomes

The following predictors were registered:

2.5.1 Clinical predictors: age, gender, Trial of Org 10172 in Acute Stroke Treatment (TOAST) subgroups[239], NIHSS on admission, occurrence of post-stroke seizures[93,142,145] (either acute symptomatic: in the first 7 days after stroke[142] or unprovoked: after that time point[145]), and *status epilepticus*[245–247]

2.5.2 Neuroimaging predictors: ASPECTS in the 1st and 2nd CT scans and any type of haemorrhage transformation[242] in the 2nd CT scan

2.5.3 EEG predictors (categorical variables, dichotomized in present or absent): background activity slowing[211]; asymmetry[212]; suppression (focal, hemispheric or diffuse)[212]; focal slow wave activity (including focal and regional concept)[211]; rhythmic slow wave activity, including rhythmic delta activity definition by the American Clinical Neurophysiology Society (ACNS)[212] and rhythmic delta/theta (>0.5 Hz)[245], interictal epileptiform activity[211] and periodic discharges[212]

The outcomes in this study were an unfavourable functional outcome (mRS≥3) and death (mRS=6) at discharge and 12 months after stroke.

2.6. Statistical Analysis

A descriptive analysis was used for nominal qualitative and quantitative variables (discrete and continuous). Nominal variables are expressed in frequency, discrete variables as medians and interquartile ranges (IQR) and continuous variables as means and standard deviations (SD).

Bivariate analysis of dichotomous data was performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate. Variables with a significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke[39–42], namely age, clinical stroke severity (admission NIHSS) and imaging infarct size (ASPECTS), using a logistic regression model. The significance level was $\alpha \leq 0.05$. Odds ratios (ORs) and 95% confidence interval (95%CIs) were calculated.

Outcome prediction model characteristics encompassing post-stroke seizures or EEG abnormalities with the highest odds to impact outcome were compared with the model including exclusively known stroke outcome predictors. The percentage of patients correctly identified by the models, was calculated. Models calibration was analysed using the Hosmer-Lemeshow test and its discriminative capacity measured by the area under the ROC curve (95%CI).

Statistical analysis was done using SPSS program version 24 for Mac.

3. RESULTS

One hundred and fifty-one patients (112 men and 39 women) were included, with a mean age of 67.4 (SD 11.9) years. During this study 23 patients died (seven during admission before day 7, 11 between discharge and 6 months after stroke and five after that time point). One patient (0.66%) was lost for clinical and EEG follow-up in the last 6 months of the study. From the 127 living patients with a clinical follow-up one-year after stroke, 117 (92.1%) had repeated EEG by that time. Study flowchart was previously described[271] (**Figure 8**). All (151) patients had at least one acute CT scan (1st CT). Furthermore, in the acute phase, a 2nd CT scan was performed in 129 (85.4%) patients and an MRI in 63 (41.7%) patients. From the 129 patients who performed a 2nd CT scan, only 124 had an isolated MCA infarct.

3.1. Variables associated with stroke outcome at discharge

Table 18 describes clinical, imaging and neurophysiological features of included patients, comparing unfavourable outcome (mRS≥3) patients with those with a favourable one (mRS<3), at discharge. In bivariate analysis, an unfavourable outcome was more frequent in older patients, patients with a higher admission NIHSS, a lower ASPECTS, presence of haemorrhagic transformation and an EEG with background activity slowing, asymmetry, focal slow wave activity and periodic discharges. After adjustment of these variables for known functional outcome predictors of stroke, admission NIHSS, EEG background activity slowing, asymmetry and periodic discharges predicted functional outcome. 2nd (but not 1st) CT ASPECTS was an independent discharge outcome predictor from age and NIHSS.

Table 18. Clinical, imaging and neurophysiological features and discharge functional outcome of anterior circulation ischaemic stroke patients

At discharge	**Modified Rankin scale score <3**	**Modified Rankin scale score ≥3**	**Bivariate analysis**[i] p OR[k]; 95% CI[l]	**Multivariate analysis**[j] p OR; 95% CI
Clinical Features (n=151)				
Number of patients	52	99		
Male (%)	29 (55.8%)	60 (60.4%)	0.566	NA
Mean Age (SD[a])	64.48 (13.20)	68.86 (10.97)	**0.032**	0.246 1.02; 0.99-1.06
Median admission NIHSS[b] (IQR[c])	8 (6)	15 (10)	**0.001**	**<0.001** 1.18; 1.10-1.28
IV alteplase	31 (59.6%)	70 (70.7%)	0.169	NA

At discharge		**Modified Rankin scale score <3**	**Modified Rankin scale score ≥3**	**Bivariate analysis**[i] p	**Multivariate analysis**[j] p OR; 95% CI
Stroke Aetiology:	Cardio-embolism	21 (40.4%)	56 (56.6%)		
	Atherosclerosis	16 (30.8%)	21 (21.2%)		
	Small vessels	2 (3.8%)	2 (2.0%)	NA	NA
	Unknown	13 (25.0%)	16 (16.2%)		
	Other	0 (0%)	4 (4.0%)		
Acute symptomatic seizures		4 (7.7%)	18 (18.2%)	0.094	NA
Non-convulsive status epilepticus		0 (0%)	4 (4%)	0.229	NA
Imaging features I					
Isolated MCA[d] **territory infarct patients with a 1st CT** (n=146)					
Number of patients		50	96		
Median ASPECTS[e] (IQR[c])		10 (1)	9 (3)	**0.042**	0.203 0.84; 0.63-1.10

At discharge	**Modified Rankin scale score <3**	**Modified Rankin scale score ≥3**	**Bivariate analysis**[i] p	**Multivariate analysis**[j] p OR; 95% CI
Imaging features II				
Isolated MCA[d] **territory infarct patients with a 2nd CT** (n=124)				
Number of patients	35	89		
Median ASPECTS[e] (IQR[c])	8 (2)	5 (4)	**0.001**	0.001 0.61; 0.47-0.80
Anterior circulation ischaemic stroke patients with a 2nd CT (n=129)				
Number of patients	37	92		
Haemorrhagic transformation	2 (5.4%)	21(22.8%)	**0.021**	0.171 3.02; 0.62-14.73

At discharge	**Modified Rankin scale score <3**	**Modified Rankin scale score ≥3**	**Bivariate analysis**[i] p	**Multivariate analysis**[j] p OR; 95% CI
1st EEG findings (n=151)				
Number of patients	52	99		
Background activity slowing	6 (11.5%)	51 (51.5%)	**0.001**	**0.002** 5.55; 1.89-16.33
Background activity asymmetry	4 (7.7%)	60 (60.6%)	**0.001**	**0.001** 11.91; 3.73-38.46
EEG suppression	1 (1.9%)	11 (11.1%)	0.059	NA
FSWA[f]	42 (80.8%)	92 (92.9%)	**0.025**	0.736 1.24; 0.36-4.24
RSWA[g]	5 (9.6%)	21 (21.2%)	0.073	NA
Periodic discharges	1 (1.9%)	26 (26.3%)	**0.001**	**0.027** 10.39; 1.30-83.03
IEA[g]	2 (3.8%)	14 (14.1%)	0.056	NA

Legend to table 18: [a]SD - standard deviation; [b]NIHSS - National Institutes of Health Stroke Scale; [c]IQR -Interquartile range; [d]MCA - middle cerebral artery; [e]ASPECTS - Alberta Stroke Program Early CT Score; [f]FSWA - focal slow wave activity; [g]RSWA - rhythmic slow wave activity; [h]IEA - interictal epileptiform activity; [i]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate; [j]Multivariate analysis - variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS) and imaging infarct severity (ASPECTS), using a logistic regression model. 1st CT ASPECTS was used except in the model including 2nd CT ASPECTS. The OR for NIHSS, age and ASPECTS are derived from multivariable logistic models including exclusively these three variables, whereas the OR for the EEG variables are derived from models including NIHSS, age, ASPECTS and the respective EEG variable; [k]OR - odds ratio; [l]CI – confidence interval; bold values - $p<0.05$

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG background activity asymmetry (**Table 19**), the variables that remained as independent predictors were NIHSS score (OR 1.16, 95%CI 1.07-1.27, p=0.001) and background activity asymmetry (OR 11.90, 95%CI 3.73-38.46, p<0.001). This model correctly classified 76.7% of the subjects and the area under the ROC curve was 0.86. The prediction model including this EEG variable did not have a different discriminative capacity compared to the model encompassing the already known outcome predictors.

Clinical, imaging and neurophysiological features of patients who died during hospitalization can be seen in **Table 20**. In bivariate analysis an association was found with admission NIHSS, occurrence of acute symptomatic seizures and EEG background activity slowing and suppression. Adjustment for known functional outcome predictors of stroke was not performed due to the low number of events (n=7)

Table 19. Comparison between stroke outcome (mRS≥3) prediction models characteristics at discharge

Logistic regression models for an unfavourable outcome (mRS≥3) at discharge									
Model Features	Omnibus Test[c]	Nagelkerke's R^2 [d]	Hosmer & Lemeshow Test[e]	PAC[f]	SEN[g]	SPE[h]	PPV[i]	NPV[j]	AUC[k] 95%CI[l]
Independent variables included in the model:									
KP[a]	$\chi^2(3)=34.85$; p<0.001	29.4%	$\chi^2(8)=4.86$; p=0.773	73.3%	85.4%	50.0%	76.6%	64.1%	0.78 0.70-0.86
EEG[b]	$\chi^2(1)=44.86$; p<0.001	35.5%	$\chi^2(0)=0.00$	71.5%	60.6%	92.3%	93.8%	55.2%	0.76 0.69-0.84
KP[a] + EEG[b]	$\chi^2(4)=59.25$; p<0.001	46.1%	$\chi^2(8)=3.67$; p=0.885	76.7%	81.3%	68.0%	83.0%	65.4%	0.86 0.79-0.92

Legend to table 19: [a]KP - known stroke outcome predictors: age, admission NIHSS and ASPECTS; [b]EEG - background activity asymmetry (EEG variable with the highest odds to impact outcome (please refer to table 1); [c]Omnibus Test - omnibus test of model coefficients (provides the overall statistical significance of the model i.e., how well the models predicts outcome to no independent variables); [d]Nagelkerke's R^2 - Nagelkerke's R square (method of calculating the explained variation. i.e., how much variation of the outcome can be explained by the model); [e]Hosmer & Lemeshow Test - Hosmer & Lemeshow goodness of fit test (analyse how poor the model is at predicting outcome. When not significant indicates that the model is not a poor fit); [f]PAC - percentage accuracy in classification (% of cases correctly classified by the model); [g]SEN - sensitivity; [h]SPE - specificity; [i]PPV - positive predictive value; [j]NPV - negative predictive value; [k]AUC - area under (receiving operator) curve; [l]CI - confidence interval

Table 20. Clinical, imaging and neurophysiological features and vital outcome of anterior circulation ischaemic stroke patients at discharge

At discharge	**Death**	**Alive**	**Bivariate analysis**[i] p
Clinical Features (n=151)			
Number of patients	7	144	
Male (%)	5 (71.4%)	84 (58.3%)	0.701
Mean Age (SD[a])	71.14 (8.80)	67.17 (12.06)	0.391
Median admission NIHSS[b] (IQR[c])	20 (9)	12 (10)	**0.032**
IV alteplase	5 (71.4%)	96 (66.7%)	1.000
Stroke Aetiology:			
Cardio-embolism	1 (14.3%)	76 (52.8%)	NA
Atherosclerosis	1 (14.3%)	36 (25.0%)	
Small vessels	0 (0%)	4 (2.8%)	
Unknown	5 (71.4%)	24 (16.7%)	
Other	0 (0%)	4 (2.8%)	
Acute symptomatic seizures	6 (85.7%)	16 (11.1%)	**<0.001**
Non-convulsive *status epilepticus*	1 (14.3%)	3 (2.1%)	0.175
Imaging Features I			
Isolated MCA[d] territory infarct patients with a 1st CT (n=146)			
Number of patients	6	140	
Median ASPECTS[e] (IQR)	8.5 (5)	9 (2)	0.343

Imaging Features II			
Isolated MCA[d] territory infarct patients with a 2nd CT(n=124)			
Number of patients	5	119	
Median ASPECTS[e] (IQR[c])	3 (7)	6 (4)	0.125
Anterior circulation ischaemic stroke patients with a 2nd CT (n=129)			
Number of patients	6	123	
Haemorrhagic transformation	1 (16.7%)	22 (17.9%)	1.000
1st EEG findings (n=151)			
Number of patients	7	144	
Background activity slowing	7 (100%)	50 (34.7%)	**0.001**
Background activity asymmetry	5 (71.4%)	59 (41.0%)	0.135
EEG suppression	4 (57.1%)	8 (5.6%)	**0.001**
FSWA[f]	6 (85.7%)	128 (88.9%)	0.574
RSWA[g]	2 (28.6%)	24 (16.7%)	0.346
Periodic discharges	2 (28.6%)	25 (17.4%)	0.609;
IEA[g]	1 (14.3%)	15 (10.4%)	0.551

Legend to table 20: [a]SD - standard deviation; [b]NIHSS - National Institutes of Health Stroke Scale; [c]IQR - interquartile Range; [d]MCA - middle cerebral artery; [e]ASPECTS - Alberta Stroke Program Early CT Score; [f]FSWA - focal slow wave activity; [g]RSWA - rhythmic slow wave activity; [h]IEA - interictal epileptiform activity; [i]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate; bold values - $p<0.05$

3.2. Variables associated with stroke outcome at 12 months

Table 21 describes clinical, imaging and neurophysiological features of included patients, comparing those with an unfavourable (mRS≥3) and favourable outcome (mRS<3). An association with an unfavourable outcome was found in bivariate analysis for age, admission NIHSS, treatment with intravenous alteplase, occurrence of an acute symptomatic or unprovoked seizure, ASPECTS and EEG background activity slowing, asymmetry, suppression, focal and rhythmic slow wave activity, periodic discharges and interictal epileptiform activity. After adjustment for known functional outcome predictors of stroke age, admission NIHSS, occurrence of an unprovoked seizure and EEG background activity slowing, asymmetry and periodic discharges remained significant. 2nd (but not 1st) CT ASPECTS was an independent discharge outcome predictor from age and NIHSS.

Table 21. Clinical, imaging and neurophysiological features and functional outcome at 12 months of anterior circulation ischaemic stroke patients

At 12 months after stroke	**Modified Rankin scale score <3**	**Modified Rankin scale score ≥3**	**Bivariate analysis**[i] p	**Multivariate analysis**[j] p OR[k]; 95% CI[l]
Clinical Features (n=150)				
Number of patients	73	77		
Male (%)	40 (54.8%)	48 (62.3%)	0.348	NA
Mean Age (SD[a])	63.45 (12.19)	71.23 (10.37)	**<0.001**	**0.001** 1.07; 1.03-1.12
Median admission NIHSS[b] (IQR[c])	9 (8)	17 (9)	**<0.001**	**0.001** 1.18; 1.1-1.28
IV alteplase	43 (58.9%)	58 (75.3%)	**0.032**	0.407 1.41;0.59-3.74

At 12 months after stroke		**Modified Rankin scale score <3**	**Modified Rankin scale score ≥3**	**Bivariate analysis**[i] p	**Multivariate analysis**[j] p OR[k]; 95% CI[l]
Stroke Aetiology:	Cardio-embolism	34 (46.6%)	43 (55.8%)		
	Atherosclerosis	18 (24.7%)	18 (23.4%)		
	Small vessels	3 (4.1%)	1 (1.3%)	NA	NA
	Unknown	16 (21.9%)	13 (16.9%)		
	Other	2 (2.7%)	2 (2.6%)		
Acute symptomatic seizures		5 (6.8%)	17 (22.1%)	**0.008**	0.220 2.19; 0.63-7.66
Non-convulsive *status epilepticus*		0 (0%)	4 (5.2%)	0.121	NA
Unprovoked seizures		5 (6.8%)	18 (25.7%)	**0.002**	**0.046** 3.76; 1.02-13.83
Seizures anytime during the study		9 (12.3%)	29 (37.7%)	**0.001**	0.128 2.19**;** 0.80-6.04

At 12 months after stroke	**Modified Rankin scale score <3**	**Modified Rankin scale score ≥3**	**Bivariate analysis[i]** p	**Multivariate analysis[j]** p OR[k]; 95% CI[l]
Imaging Features I				
Isolated MCA[d] territory infarct patients with a 1st CT (n=145)				
Number of patients	71	74		
Median ASPECTS[e] (IQR)	10 (1)	9 (3)	**0.029**	0.089 0.90; 0.61-1.04
Isolated MCA[d] territory infarct patients with a 2nd CT (n=124)				
Number of patients	54	70		
Median ASPECTS[e] (IQR[c])	8 (3)	4.5 (5)	**<0.001**	OR 0.68 95%CI 0.54-0.84 p=0.001

Imaging Features II				
Anterior circulation ischaemic stroke patients with a 2nd CT (n=129)				
Number of patients	56	73		
Haemorrhagic transformation	7 (12.5%)	16 (21.9%)	0.166	NA
1st EEG findings I (n=150)				
Number of patients	73	77		
Background activity slowing	7 (9.6%)	50 (64.9%)	**<0.001**	**0.001** 14.50; 4.95-42.48
Background activity asymmetry	8 (11.0%)	56 (72.7%)	**<0.001**	**0.001** 22.73; 7.30-71.43
EEG suppression	1 (1.4%)	10 (13.0%)	**0.009**	0.09 8.85; 0.71- 110.22
FSWA[f]	60 (82.2%)	73 (94.8%)	**0.020**	0.534 1.60; 0.36- 7.02

1st EEG findings II (n=150)				
RSWA[g]	8 (11.0%)	18 (23.4%)	**0.045**	0.086 2.58; 0.88-7.64
Periodic discharges	2 (2.7%)	25 (32.5%)	**<0.001**	**0.002** 14.10; 2.73-72.78
IEA[g]	3 (4.1%)	13 (16.9%)	**0.016**	0.153 3.03; 0.66-13.86

Legend to table 21: [a]SD - standard deviation; [b]NIHSS – National Institutes of Health Stroke Scale ; [c]IQR - interquartile Range; [d]MCA - middle cerebral artery; [e]ASPECTS - Alberta Stroke Program Early CT Score; [f]FSWA - focal slow wave activity; [g]RSWA - rhythmic slow wave activity; [h] IEA - interictal epileptiform activity; [i]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate; [j]Multivariate analysis - variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS) and imaging infarct severity (ASPECTS), using a logistic regression model. 1st CT ASPECTS was used except in the model including 2nd CT ASPECTS. The OR for NIHSS, age and ASPECTS are derived from multivariable logistic models including exclusively these three variables, whereas the OR for the EEG variables are derived from models including NIHSS, age, ASPECTS and the respective EEG variable"; [k]OR - odds ratio; [l]CI – confidence interval; bold values - $p<0.05$

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG asymmetry (**Table 22A**), the variables remaining independent predictors were age (OR 1.09, 95%CI 1.09-1.04, p=0.001), NIHSS score (OR 1.18, 95%CI 1.07-1.29, p=0.001) and EEG background activity asymmetry (OR 22.73, 95%CI 7.30-71.43, p<0.001). This model correctly classified 84.8% of the subjects and the area under the ROC curve was 0.91. The prediction model including this EEG variable did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

In the logistic regression model encompassing known functional outcome predictors of stroke and unprovoked seizures (**Table 22A**), the variables remaining independent predictors were age (OR 1.08, 95%CI 1.04-1.14, p<0.001), NIHSS score (OR 1.18, 95%CI 1.09-1.28, p<0.001) and unprovoked seizures (OR 3.76, 95%CI 1.02-13.83, p=0.046). This model correctly classified 74.8% of the subjects and the area under the ROC curve was 0.83. The prediction model including this type of post-stroke seizures did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

Clinical, imaging and neurophysiological features of patients who died in the first year after stroke are disclosed in **Table 23**. An association with death in the first year after stroke was found in bivariate analysis for age, admission NIHSS, occurrence of an acute symptomatic seizure and EEG background activity slowing, asymmetry, suppression and periodic discharges. After adjustment for known functional outcome predictors of stroke age, admission NIHSS, occurrence of an acute symptomatic seizure and EEG suppression remained significant.

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG suppression (**Table 22B**), the variables remaining independent predictors were age (OR 1.06, 95%CI 1.01-1.12, p=0.032), NIHSS score (OR 1.18, 95%CI 1.07-1.31, p=0.001) and EEG suppression (OR 7.48, 95%CI 1.40-39.99, p=0.019). This model correctly classified 89.0% of the subjects and the area under the ROC curve was 0.84. The prediction model including this EEG variable did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

In the logistic regression model encompassing known functional outcome predictors of stroke and acute symptomatic seizures (**Table 22A**), the variables remaining independent predictors were age (OR 1.06, 95%CI 1.00-1.12, p=0.039), NIHSS score (OR 1.19, 95%CI 1.07-1.31, p=0.001) and acute symptomatic seizures (OR 4.55, 95%CI 1.34-15.47, p=0.015). This model correctly classified 91.0% of the subjects and the area under the ROC curve was 0.82. The prediction model including this type of post-stroke seizures did not have a different discriminative capacity compared to the model encompassing the already known outcome predictors.

Table 22. Comparison between stroke outcome (mRS≥3 and mRS=6) prediction models characteristics at 12 months

A. Logistic regression models for an unfavourable outcome (mRS≥3) at 12 months									
Model Features	Omnibus Test	Nagelkerke's R^2	Hosmer & Lemeshow Test	PAC[a]	SEN[b]	SPE[c]	PPV[d]	NPV[e]	AUC[f] 95%CI[g]
Independent variables included in the model:									
KP[a]	$\chi^2(3)=52.00$; p<0.001	40.2%	$\chi^2(8)=3.46$; p=0.902	71.7%	70.3%	73.2%	73.2%	70.3%	0.82 0.75-0.88
EEG[b]	$\chi^2(1)=64.00$; p<0.001	46.3%	$\chi^2(0)=0.00$	80.7%	72.7%	89.0&	87.5%	75.6%	0.81 0.74-0.88
KP[a] +EEG[b]	$\chi^2(4)=93.52$; p<0.001	63.4%	$\chi^2(8)=4.38$; p=0.82	84.8%	81.1%	88.7%	88.2%	81.8%	0.91 0.86-0.96
US[c]	$\chi^2(1)=9.88$; p=0.002	8,9%	$\chi^2(0)=0.00$	60.1%	25.7%	93.2%	78.3%	56.7%	0.59 0.50-0.69
KP[a] + US[c]	$\chi^2(4)=54.62$; p<0.001	43.3%	$\chi^2(8)=3.74$ p=0.88	74.8%	72.1%	77.5%	75.4%	74.3%	0.83 0.77-0.90

B. Logistic regression models for death (mRS=6) at 12 months									
Model Features:	Omnibus Test	Nagelkerke's R^2	Hosmer & Lemeshow Test	PAC[d]	SEN[e]	SPE[f]	PPV[g]	NPV[h]	AUC[i] 95%CI[j]
Independent variables included in the model:									
KP[a]	$\chi^2(3)=25.58$; p<0.001	28.2%	$\chi^2(8)=12.71$; p=0.122	86.9%	22.7%	98.4%	71.4%	87.7%	0.81 0.70-0.92
EEG[d]	$\chi^2(1)=10.10$; p=0.001	11,3%	$\chi^2(0)=0$,00	85.3%	26.1%	96.1%	54.5%	87.8%	0.61 0.47-0.75
KP[a] +EEG[d]	$\chi^2(4)=31.21$; p<0.001	33.8%	$\chi^2(8)=15.39$; p=0.052	89.0%	31.8%	99.2%	87.5%	89.1%	0.84 0.74-0.93
ASS[e]	$\chi^2(1)=10.394$; p=0.001	11.6%	$\chi^2(0)=0,00$	84.7%	0%	100%	0%	84.7%	0.64 0.51-0.78
ASS[e]+ KP[a]	$\chi^2(4)=31.31$; p<0.001	33.9%	$\chi^2(8)=20.62$; p=0.008	91.0%	40.9%	100%	100%	90.4%	0.82 0.70-0.94

Legend to table 22: [a]KP - known stroke outcome predictors: age, admission NIHSS and ASPECTS; [b]EEG - background activity asymmetry (EEG variable with the highest odds to impact functional outcome (please refer to table 4); [c]US - unprovoked seizures; [d]EEG - EEG suppression (EEG variable with the highest odds to impact vital outcome (please refer to table 6); [e]ASS - acute symptomatic seizures; [f] Omnibus Test - omnibus test of model coefficients (provides the overall statistical significance of the model i.e. how well the models predicts outcome to no independent

variables); [g]Nagelkerke R^2 – Nagelkerke's R square (method of calculating the explained variation. i.e. how much variation of the outcome can be explained by the model); [h]Hosmer & Lemeshow Test - Hosmer & Lemeshow goodness of fit test (analyse how poor the model is at predicting outcome. When not significant indicates that the model is not a poor fit); [i]PAC- percentage accuracy in classification (% of cases correctly classified by the model); [j]SEN – sensitivity; [k]SPE – specificity; [l]PPV - positive predictive value; [m]NPV - negative predictive value; [n]AUC - area under (receiving operator) curve; [o]95% CI - 95% confidence interval

Table 23. Clinical, imaging and neurophysiological features and vital outcome at 12 months of anterior circulation ischaemic stroke patients

At 12 months after stroke	**Death**	**Alive**	**Bivariate analysis**[i] p	**Multivariate analysis**[j] OR[k]; 95% CI
Clinical Features (n=150)				
Number of patients	23	127		
Male (%)	15 (65.2%)	73 (57.5%)	0.488	NA
Mean age (SD[a])	73.74 (10.08)	66.31(11.90)	**0.006**	**0.028** 1.06; 1.01-1.12
Median admission NIHSS[b] (IQR[c])	18 (7)	11(10)	**<0.001**	**0.001** 1.18; 0.70-1.30
IV alteplase	18 (78.3%)	83 (65.4%)	0.225	NA
Stroke Aetiology: Cardio-embolism	10 (43.5%)	67 (52.8%)	NA	NA
Atherosclerosis	5 (21.7%)	31 (24.4%)		
Small vessels	0 (0%)	4 (3.1%)		
Unknown	8 (34.8%)	21 (16.5%)		
Other	0 (0%)	4 (3.1%)		

At 12 months after stroke	**Death**	**Alive**	**Bivariate analysis**[i] p	**Multivariate analysis**[j] OR[k]; 95% CI
Acute symptomatic seizures	9 (39.1%)	13 (10.2%)	**<0.001**	**0.015** 4.55; 1.34-15.47
Non-convulsive *status epilepticus*	1 (4.3%)	3 (2.4%)	0.587	NA
Unprovoked seizures	1 (6.3%)	22 (17.3%)	0.469	NA
Imaging Features				
Isolated MCA[d] **territory infarct patients with a 1st CT** (n=145)				
Number of patients	22	123		
Median ASPECTS[e] (IQR)	9 (4)	9 (2)	0.295	NA
Anterior circulation ischaemic stroke patients with a 2nd CT (n=129)				
Number of patients	22	107		
Haemorrhagic transformation	2 (9.1%)	21(19.6%)	0.362	NA

At 12 months after stroke	**Death**	**Alive**	**Bivariate analysis[i]** p	**Multivariate analysis[j]** OR[k]; 95% CI
1st EEG findings (n=150)	23	127		
Background activity slowing	16 (69.6%)	41 (32.3%)	**0.001**	0.219 1.99; 0.66-5.99 0.219
Background activity asymmetry	16 (69.6%)	48 (37.8%)	**0.005**	0.495 1.48, 0.48-4.50 0.495
EEG suppression	6 (26.1%)	5 (3.9%)	**<0.001**	**<0.019** 7.48; 1.40-39.99
FSWA[f]	22 (95.7%)	111 (87.4%)	0.251	NA
RSWA[g]	5 (21.7%)	21 (16.5%)	0.544	NA
Periodic discharges	8 (34.8%)	19 (15.0%)	**0.023**	0.464; 1.54; 0.48-4.94
IEA[g]	3 (13.0%)	13 (10.2%)	0.688	NA

Legend to table 23: [a]SD - standard deviation; [b]NIHSS – National Institutes of Health Stroke Scale; [c]IQR - interquartile range; [d]MCA - middle cerebral artery; [e]ASPECTS - Alberta Stroke Program Early CT Score; [f]FSWA - focal slow wave activity; [g]RSWA - rhythmic slow wave activity ; [h]IEA - interictal epileptiform activity; [i]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact

test and quantitative variables by t-test or Mann-Whitney U, as appropriate; [j]Multivariate analysis - variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS) and imaging infarct severity (ASPECTS), using a logistic regression model. The OR for NIHSS, age and ASPECTS are derived from multivariable logistic models including exclusively these three variables, whereas the OR for the EEG variables are derived from models including NIHSS, age, ASPECTS and the respective EEG variable"; [i]SD - standard deviation; [k]OR - odds Ratio; [l]CI - confidence interval

4. DISCUSSION

In this work, acute symptomatic seizures were independent predictors of death and unprovoked seizures independent predictors of an unfavourable outcome in the first year after an anterior circulation ischaemic stroke. We also demonstrated that EEG abnormalities extracted from visual analysis of a single, early (<72 hours after stroke) and short duration EEG, are strong predictors of functional outcome, even when adjusted for previously known (early clinical and imaging) stroke outcome predictors.

We think that the strengths of this work, standing out from previous research in this area, include the sample size of consecutive anterior circulation stroke patients, the prospective nature of a multimodal (clinical, neurophysiological and imagiological) study and the 12 months follow-up with only one patient lost during this period, as well as, the adjustment to clinical and infarct severity.

As a limitation, we did not analyse the value of EEG as a functional outcome predictor compared with 2nd CT scan or brain MRI, avoiding the inclusion of variables with a high percentage of missing data (17.9% and 58.3%, respectively) in our regression models. Sillipaa et al.[279] showed the superior of ASPECTS quantified at 24h after stroke (over on-admission) non-contrast-enhanced CT in outcome prediction. In our analysis, 2nd CT ASPECTS (but not 1st CT ASPECTS) was a predictor of stroke functional outcome independently from age and admission NIHSS. Nevertheless, this result must be cautiously interpreted because of the missing data. We acknowledge that our 1st CT ASPECTS median reflects the difficulty of estimating stroke size from early non-contrast-enhanced CT reducing the value of this score in functional outcome assessment. Nevertheless, in the clinical practice of a significant proportion of Stroke Units (such as ours), a 2nd CT scan is not routinely performed in all patients, unless they had been treated with intravenous alteplase or had a neurological worsening. In our study, using an easy, non-invasive, short duration and bedside EEG examination, available in the great majority of neurological departments and intensive care units, we identified neurophysiological independent predictors of stroke outcome in models already including well-established clinical and early imaging outcome prognostic factors.

4.1. Post-stroke seizures and stroke outcome

In our bivariate analysis, seizures were associated with an unfavourable functional outcome one year after stroke, as previously suggested in the literature[44,45,80,280]. It has been postulated in the animal model that post-stroke seizures may contribute to tissue damage[281,282]. In addition, De Reuck et al.[79] showed that unprovoked seizures are associated with lesion increase and worsening of disability. As a novel finding, we show that the association between unprovoked seizures and an unfavourable functional outcome 12 months after stroke does remain significant when adjusted for age, clinical and imaging stroke severity. Furthermore, in our work, acute symptomatic seizures remained as an independent predictor of death in the first year after an anterior circulation stroke, even after adjustment for known stroke outcome predictors**.** Hesdorffer et al.[44] similarly showed that patients with acute symptomatic seizures (of different aetiologies) had an 8.9 times higher chance of dying within 30 days. More recently, Huang et al.[45] also found that patients with seizures during admission for stroke had a higher mortality at 30 days and 1 year. This finding was not observed in Hamidou et al. study[283] using, however, a population based registry and a different definition of early seizures.

4.2. EEG abnormalities and stroke outcome

EEG background activity slowing was associated with stroke clinical severity by Kayer-Gatchalian and collaborators[85] and, as in our study, with an unfavourable stroke outcome by Cillessen et al.[87]. The originality of our study resides in the definition of electroencephalographic independent predictors of stroke functional outcome, either at short and at long term, even when adjusted for age and clinical and imaging severity of stroke.

The neurophysiological feature with the highest odds to impact functional outcome was background activity asymmetry. Quantitative EEG studies support our observation. Brain symmetry index (BSI) obtained from continuous EEG records has been correlated with NIHSS score[62] and lesion volume in MRI[284]. In an easier and more simply way, we showed that background activity asymmetry in raw analysis of a single and short duration EEG, is an independent predictor of an unfavourable stroke outcome. Cuspineda and collaborators, using quantitative EEG in 28 patients, showed that this is better than the Canadian Neurological Scale score in residual functional disability prediction[89] and than mRS in the prediction of functional outcome[89,285]. In our study, the prognostic models including raw

EEG abnormalities correctly classified a higher percentage of patients than the model including exclusively the already known stroke outcome predictors. We believe that our results show that some early electroencephalographic characteristics are comparable to the clinical stroke severity and better than early CT infarct severity in the determination of post-stroke functional outcome and reflects the concept that the EEG is a sensitive neurological diagnosis technique in the detection of acute cerebral ischaemia[36] and a robust one in the functional assessment of the brain[37].

The association between EEG suppression and death deserves attention. Even though the low number of patients who died in the hospital does not allow a multivariate analysis, this neurophysiological characteristic has been associated with larger infarcts with a higher risk of becoming malignant[64], and may draw attention to the need for an early start of medical and/or surgery therapy. In line with our results on focal cerebral ischaemia outcome, EEG suppression was recently ranked within malignant EEG patterns and as a poor prognostic predictor of post-cardiac arrest diffuse cerebral ischaemia[286]. Indeed, in our study, this electroencephalographic feature was an independent predictor of the vital outcome one year after stroke when controlled for age and stroke severity.

XII. PROJECT 9

"But the electroencephalogram can detect changes in brain activity a thousand times faster than most biochemical indices, and they are not measures of cell metabolism but the summation of cortical postsynaptic potentials themselves,
a distant eavesdrop on the brain's inner workings"
Fernando Lopes da Silva

QUANTITATIVE EEG AND FUNCTIONAL OUTCOME FOLLOWING ACUTE ANTERIOR ISCHAEMIC STROKE

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Objective: To identify the most accurate quantitative electroencephalographic (qEEG) predictor(s) of unfavourable post-ischaemic stroke outcome, and its(their) discriminative capacity compared to already known demographic, clinical and imaging prognostic markers.

Methods: Prospective cohort of 151 consecutive anterior circulation ischemic stroke patients followed for 12 months. EEG was recorded within 72 hours and at discharge or 7 days post-stroke. QEEG (global band power, symmetry, affected/unaffected hemisphere and time changes) indices were calculated from mean Fast Fourier Transform and analysed as predictors of unfavourable outcome (mRS≥3), at discharge and 12 months poststroke, before and after adjustment for age, admission NIHSS and ASPECTS.

Results: Higher delta, lower alpha and beta relative powers (RP) predicted outcome. Indices with higher discriminative capacity were delta-theta to alpha-beta ratio (DTABR) and alpha RP. Outcome models including either of these and other clinical/imaging stroke outcome predictors were superior to models without qEEG data. In models with qEEG indices, infarct size was not a significant outcome predictor.

Conclusions: DTAABR and alpha RP are the best qEEG indices and superior to ASPECTS in post-stroke outcome prediction. They improve the discriminative capacity of already known clinical and imaging stroke outcome predictors, both at discharge and 12 months after stroke.

Significance: qEEG indices are independent predictors of stroke outcome.

KEY-WORDS

ischaemic stroke, functional outcome, quantitative EEG, alpha relative power, delta-theta to alpha-beta ratio

1. INTRODUCTION

Stroke is a leading cause of disability and mortality worldwide, and despite advances in disease prevention, acute treatment and rehabilitation, global stroke burden is expected to rise in the future[287]. Early post-stroke prognostication is essential both in the short-term (e.g. in guiding treatment strategies) and in the long-term (to aid in rehabilitation management, in order to improve recovery and minimize disability). Predictors of stroke disability and associated death consistently include age and clinical / imaging related stroke severity[39–42,288–291]. However, despite the existence of demographic, clinical and imaging factors that can be associated with functional outcome, early prediction of short and long-term post-stroke outcome is challenging since there is large interindividual variability[43]. Therefore, there is still a need to identify reliable, inexpensive biomarkers that can add prognostic information in these patients. Due to accumulating evidence regarding neuro-vascular uncoupling in acute ischemic stroke, neurophysiological biomarkers seem increasingly relevant for predicting outcome[49].

EEG is a non-invasive, inexpensive diagnostic method, with high temporal resolution, contributing to a rapid evaluation of instantaneous brain function. However, its visual interpretation requires technical experience, and may be subject to interrater variability. Hence, quantitative EEG (qEEG) techniques have emerged and have been proven informative in stroke prognostication[292]. These techniques have the advantage of providing objective, rater-independent information, which can be used in a variety of settings, including intensive care units. Previous studies have also shown they can be equal to or even more informative than visual EEG interpretation for detecting cerebral pathology[58,60,293,294]. In general, EEG parameters such as total power, relative delta and alpha power, ratios between slower and faster frequencies (such as the delta/alpha ratio [DAR] and the [delta+theta/alpha+beta] ratio [DTABR]), and brain symmetry indices (such as the Brain

Symmetry Index [BSI] and pair-derived BSI) have been strongly associated with stroke outcome for up to 12 months[292]. These measures have also been shown, in some studies, to be more reliable in prognostication than standard clinical evaluation[295–299] or imaging biomarkers[298–300].

However, direct comparison of these measures and indices for predicting stroke outcome has yielded conflicting results[292]. Moreover, few previous studies attempted to control for independent known outcome factors, such as age at stroke onset, clinical severity at admission or infarct size.

Therefore, the principal objectives of this study were: 1) to identify the most accurate qEEG measure(s) associated with outcome at discharge and 12 months after stroke, 2) to compare the discriminative capacity of outcome models based exclusively on already known demographic, clinical and imaging prognostic markers and including one qEEG variable, and 3) to compare qEEG and visual EEG analysis in stroke outcome prediction, in a large, well defined cohort of acute anterior circulation ischemic stroke patients.

2. METHODS

2.1. Study design

Study design has been previously described[301]. We performed a prospective longitudinal study of consecutive anterior circulation ischaemic stroke patients admitted to the Stroke Unit of the Neurology Department of a University Hospital, over a period of 24 months (from October 2011 to October 2013) and followed for 12 months. The Ethics Committee "Comissão de Ética para a Saúde" of our hospital approved the study. All subjects or their next of kin gave written informed consent for participation. All included patients had to be previously independent (modified Rankin Scale [mRS] ≤1), have a National Institutes of Health Stroke Scale Score (NIHSS) ≥4[70] upon admission to the emergency department, have an acute ischaemic brain lesion (CT scan or MRI) in the internal carotid artery territory and no previous history of epileptic seizures nor traumatic head injury requiring hospital admission.

2.2. Clinical Assessment

All patients received standardized clinical and diagnostic assessment, during admission and after discharge. An investigator blinded to the neurophysiological evaluation conducted a phone interview at six months and a clinical appointment 12 months after stroke to access the occurrence of epileptic seizures and functional outcome. Clinical stroke severity was assessed by NIHSS at admission. The functional outcome at discharge and at 12 months was assessed by the mRS scale[236].

2.3. Neuroimaging interpretation

A senior neuroradiologist, (CM or CC) blinded for clinical and electroencephalographic findings analysed the neuroimaging studies. Doubts were decided by consensus. In patients

with middle cerebral artery stroke, infarct size was quantified by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS)[42] in an acute brain CT (computed tomography) scan performed in the first 24 hours after stroke.

2.4. Neurophysiological evaluation

Patients underwent a neurophysiological evaluation protocol that included a 64-channel video-EEG with a maximum duration of 60 minutes in the first 72 hours after stroke (first EEG). A similar EEG was also collected at discharge or on the 7th day post-stroke (second EEG). The neurophysiological protocol was previously described[302]. The record included an eyes-closed, wake resting condition and eyes-open, hyperventilation and photic stimulation activation manoeuvers. Raw EEG review was performed by a certified clinical neurophysiologist (CB) using international criteria and terminology[212,245,303], blinded for clinical and imaging findings. All doubts were decided by consensus with another clinical neurophysiologist (ARP).

2.4.1. EEG acquisition

The EEG was recorded in a Nihon-Kohden device with a sample frequency of 1000Hz. Consecutive samples of EEG, acquired in similar technical conditions (eyes closed, resting condition outside hyperventilation, photic stimulation or sleep) and with the best possible technical quality, were selected forming an EEG segment of 1-10 minutes.

2.4.2. EEG Processing

EEG segments (high cutoff filter 70 Hz; low cutoff filter 0.5 Hz; notch filter 50 Hz, average montage) were exported for FTT analysis in BESA software (BESA Research 6.0, June 2013, BESA GmbH, Graefelting, Germany). In BESA, visual and automatic rejection of

artefacts was done. When present, blinking artefacts were also removed by principal component analysis. The EEG was then segmented into 2.05 seconds mini-epochs and FFT analysis was performed for each of these segments. Mean Fast Fourier Transform (FFT) of all the 2.05 seconds mini-epochs of the selected EEG segment was computed in the following frequency bands: Delta – 1-4 Hz; Theta – 4-8 Hz; Alfa – 8-12 Hz; Beta – 12-30 Hz. Relative (RP) and absolute power (AP) in these frequency bands was obtained.

2.4.3. Computed Indices (qEEG predictors)

Several qEEG indices were calculated from both hemispheres, the affected and unaffected hemisphere, from the first and second EEG recordings, and in the frequency bands described in section 2.4.2. Details for qEEG index calculation are presented in **Appendix P.**

Computed indices were: global relative power indices including delta, theta, alpha and beta relative power, as well as ratios between slow and fast frequencies (slow (delta-theta) and fast (alfa-beta) frequencies ratio (DTABR), delta and alpha ratio (DAR)). Furthermore, symmetry indices included the brain symmetry index (BSI) and the ratio between affected and unaffected hemisphere RP. We also calculated affected and unaffected hemisphere indices. Lastly, we computed time changes indices, reflecting the dynamic changes between the first (0-72h) and second EEG (discharge or 7^{th} day post-stroke): Acute Symmetry Change Index (ASCI), Acute Delta, Alpha, Theta and Beta Change Indices, and Acute DTABR Change Index. For simplicity purposes, only results concerning the global relative power indices are reported in the main document. Results from other indices can be found in Appendix B. EEG indices were, whenever necessary, transformed to their natural logarithm or square root in order to have normal distribution and homogeneity of variances, as required for logistic regression models.

2.5. Outcomes

The outcomes in this study were an unfavourable functional outcome (mRS≥3) at discharge and 12 months after stroke.

2.6. Statistical Analysis

EEG spectral indices were evaluated using descriptive statistics (mean and standard deviation) in patients with unfavourable and favourable outcome at discharge (D1 EEG indices) and 12 months (first EEG, second EEG and dynamic EEG evolution indices) post-stroke. Bivariate analyses were performed between groups using t-test after confirming their normal distribution (Shapiro Wilk and Kolmogorov Smirnov tests) or Mann-Whitney test in non-normal variables. Prognostic models were constructed using logistic regression. Homogeneity of variances was confirmed with the Levene test, and model calibration was analysed by Hosmer-Lemeshow. QEEG variables with a significant association in the bivariate analysis were adjusted for known functional outcome predictors of stroke [39–42], namely age, clinical stroke severity (admission NIHSS) and imaging infarct size (ASPECTS). All logistic models were constructed with only one qEEG variable plus these previously known outcome predictors, in order to avoid the multicollinearity between qEEG variables. Logistic models were performed with the neurophysiological variables in their natural logarithm (Ln) or square root transformation to comply with the model requisites.

Additionally, to assess the overall internal validation of each model, a 10-fold cross-validation technique was implemented. After dividing the dataset into 10 random folds, we used N-1 (9) folds to calculate the model coefficients, which were then applied to the remaining fold to yield fitted values for these observations. The process was repeated 10 times using different folds of the data. Finally, we used the fitted values to obtain a cross-validated area under the ROC curve (cvAUC) and corresponding 95% confidence intervals.

Using DeLong tests, the outcome prediction model including the qEEG index with highest cvAUCs was compared with the model including exclusively known stroke outcome predictors, as well as with models using known predictors and visual EEG analysis variables, namely background activity asymmetry. EEG background asymmetry was chosen in accordance with a previous report where it was shown that this was the variable most strongly associated with anterior circulation ischaemic stroke outcome[274]. Cut-off values were calculated for various sensitivities and specificities. The significance level was $\alpha \leq 0.05$. Statistical analysis was performed using SPSS program version 24 for Mac, and STATA 14.2 for Mac (Statacorp®).

3. RESULTS

3.1. Study Population

One-hundred-and-fifty-one patients (112 men and 39 women) were included, with a mean age of 67.4 (SD 11.9) years. During the study period, 23 patients died (seven during admission before day 7). One patient (0.66%) was lost for clinical follow-up at 12 months. All patients had at least one acute CT scan and D1 EEG. In 8 patients, D7 EEG was not performed. One patient had bilateral middle cerebral artery stroke and was not included. Study flowchart and further details of the sample studied have been previously described[304].

3.2. Functional Outcome at discharge and at 12 months

3.2.1. Bivariate analyses

All patients were included in the analysis. The average duration of the EEG segments used for FFT calculation, after artifact removal was 248 (SD 222) seconds (median 213 seconds). **Tables 24** and **25** show the main qEEG indices calculated for patients who were alive and independent at discharge and at 12 months, respectively, as compared to patients who died or were dependent at these time points. Most qEEG indices show significant differences between these two groups. Overall, dependence or death at discharge is associated with EEGs with higher slow frequency (delta) and lower high frequency (alpha and beta) powers, both in overall EEG power and in each hemisphere separately (affected and unaffected). Further results from the bivariate analysis are found in **Appendix Q**

Table 24. Quantitative EEG indices and outcome at discharge.

qEEG index	mRS<3 (n=52)	mRS≥3 (n=99)	Bivariate analysis p	Multivariate analysis p OR (95%CI)	Cross-validated AUC (95% CI)
1st EEG (0-72h)					
Delta RP	0.37 ± 0.17 (0.37)	0.54 ± 0.17 (0.54)	<0.001*	<0.001[a] 125.0 (9.2-1692.4)	0.812 (0.740 – 0.884)
Theta RP	0.20 ± 0.08 (0.21)	0.22 ± 0.09 (0.20)	ns[+]	NA	NA
Alpha RP	0.23 ± 0.12 (0.22)	0.13 ± 0.08 (0.11)	<0.001[+]	<0.001[b] 0.221 (0.099-0.492)	0.814 (0.742 – 0.885)
Beta RP	0.20 ± 0.13 (0.18)	0.12 ± 0.08 (0.09)	<0.001[+]	<0.001[b] 0.28 (0.140-0.574)	0.803 (0.729 – 0.877)
DTABR	1.87 ± 1.45 (1.51)	4.61 ± 3.29 (4.01)	<0.001[+]	p<0.001[a] 1.702 (1.297-2.231)	0.827 (0.758 - 0.895)

Legend to table 24: Results in the 2nd and 3rd column are shown as mean ± standard deviation (median) of the natural logarithm of the EEG index. Multivariate analyses included the variables age, NIHSS at admission and ASPECTS scores plus the EEG index. CI 95% - 95% confidence interval; DTABR - delta-theta to alpha-beta ratio; OR - odds ratio; RP - relative power; NA - not applicable; *t-test; +Mann-Whitney U test; a - logistic regression using the untransformed variable; b - logistic regression using the variable transformed into the natural logarithm.

Table 25. Quantitative EEG indices and outcome at 12 months.

qEEG Index	mRS<3 (n=73)	mRS≥3 (n=77)	Bivariate analysis p	Multivariate analysis p OR (95%CI)	Cross-validated AUC (95% CI)
1st EEG (0 – 72 hours)					
Delta RP	0.41 ± 0.17 (0.40)	0.56 ± 0.17 (0.58)	<0.001*	<0.001[a] 129.8 (8.8-1904.5))	0.836 (0.771 – 0.900)
Theta RP	0.20 ± 0.09 (0.20)	0.22 ± 0.09 (0.22)	ns[+]	-	-
Alpha RP	0.21 ± 0.11 (0.17)	0.12 ± 0.08 (0.11)	<0.001[+]	<0.001[b] 0.16 (0.064-0.380)	0.852 (0.790 – 0.913)
Beta RP	0.19 ± 0.12 (0.16)	0.11 ± 0.08 (0.08)	<0.001[+]	<0.001[b] 0.28 (0.137-0.572)	0.829 (0.763 – 0.895)
DTABR	2.17 ± 1.56 (1.68)	5.12 ± 3.46 (4.15)	<0.001[+]	p<0.001[a] 1.668 (1.297-2.143)	0.859 (0.800 - 0.919)

qEEG Index	mRS<3 (n=73)	mRS≥3 (n=77)	Bivariate analysis p	Multivariate analysis p OR (95%CI)	Cross-validated AUC (95% CI)
2nd EEG (day 7 or discharge)					
Delta RP	0.37 ± 0.16 (0.33)	0.57 ± 0.19 (0.57)	<0.001+	<0.001a 165.4 (13.43-2036.1)	0.833 (0.768 - 0.899)
Theta RP	0.19 ± 0.10 (0.15)	0.20 ± 0.09 (0.18)	ns+	-	-
Alpha RP	0.24 ± 0.13 (0.22)	0.13 ± 0.10 (0.10)	<0.001+	<0.001c 0.001 (0.000-0.027)	0.827 (0.760 - 0.894)
Beta RP	0.21 ± 0.13 (0.18)	0.10 ± 0.09 (0.08)	<0.001+	<0.001b 0.319 (0.17-0.60)	0.819 (0.750 - 0.888)
DTABR	1.88 ± 1.89 (1.25)	10.64 ± 35.91 (4.15)	<0.001+	<0.001 a 3.170 (1.860-5.420)	0.843 (0.779 - 0.907)

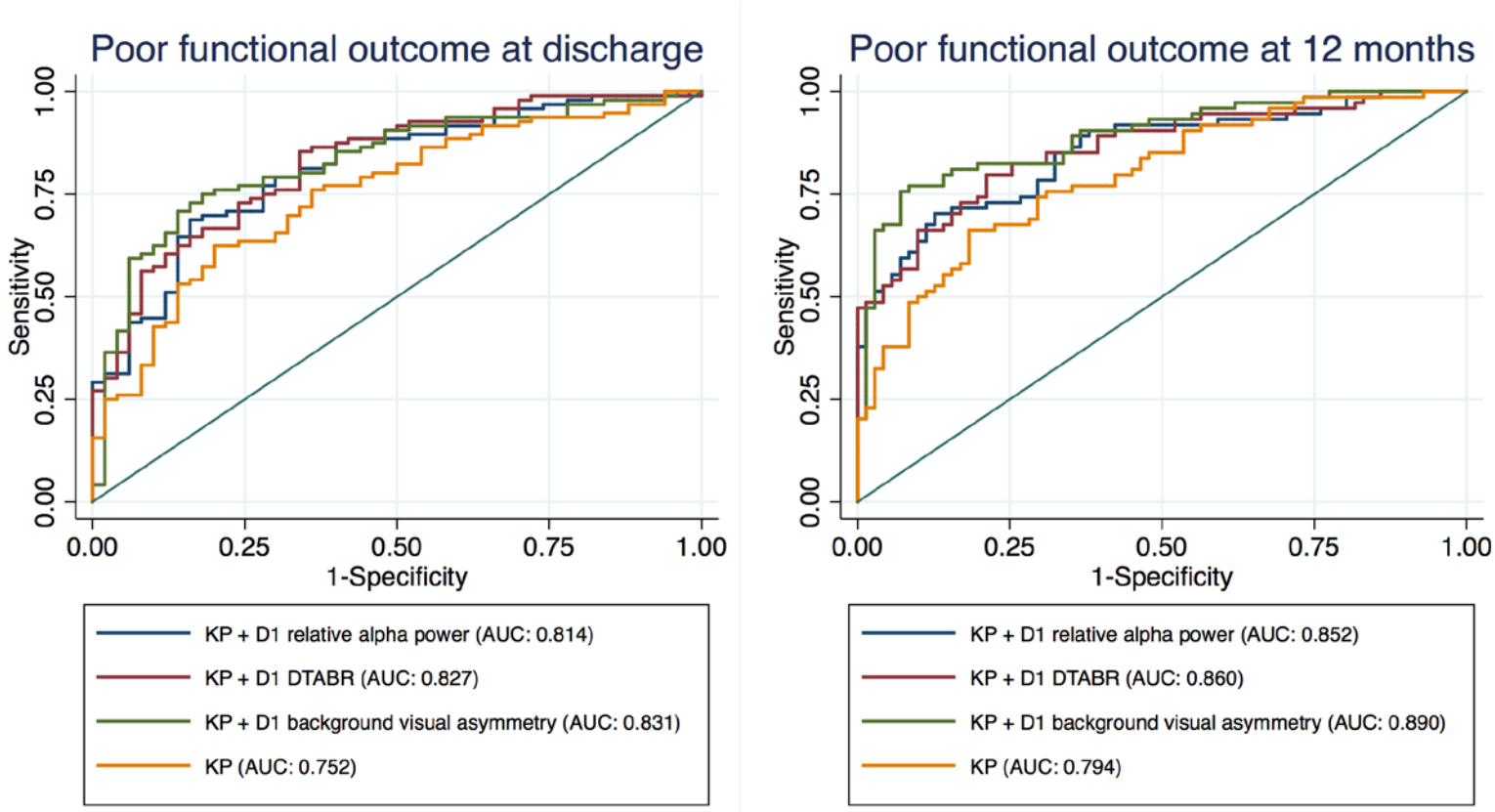
Legend to table 25: Results in the 2nd and 3rd column are shown as mean ± standard deviation (median) of the natural logarithm of the EEG index. Multivariate analyses included the variables age, NIHSS at admission and ASPECTS scores plus the EEG index. OR - odds ratio; RP - relative power; DTABR - delta-theta to alpha-beta ratio; * t-test; +Mann-Whitney U test; a - logistic regression using the untransformed variable; b - logistic regression using the variable transformed into the natural logarithm; c - logistic regression using the variable transformed into the square root.

3.2.2. Multivariate analyses

On multivariate analysis, after controlling for admission NIHSS, age and ASPECTS, most of the neurophysiological variables remained as independent predictors of outcome (**Appendix Q**).

After 10-fold cross-validation, the variables rendering models with highest cvAUC were DTABR, and alpha RP. Therefore, models including DTABR or alpha RP were chosen for ROC comparison with both the known functional outcome predictor model and the model with visual EEG analysis of background asymmetry (**Figure 13**). While DTABR is associated with the highest cvAUC both at discharge and 12 months, alpha RP was chosen because it is easy to calculate and is less prone to interference from artifacts than qEEG indices including lower frequencies.

Figure 13. Receiver Operating Characteristic (ROC) curves for multivariate models including known post-stroke outcome predictors



Legend to figure 13: KP - age, admission NIHSS and 1st CT ASPECTS, with or without one additional qEEG index (DTABR - delta-theta to alfa-beta ratio or alpha RP - relative power) obtained from the quantitative analysis of the first EEG or visual EEG analysis (background asymmetry) of the same record, in relation to poor functional outcome at discharge (A) and 12 months (B).

Table 26, displays the comparison between stroke outcome prediction models' characteristics at discharge and 12 months poststroke. For discharge outcome, compared with the known functional outcome predictors model (cvAUC 0.752, 95% CI 0.671-0.834), both models including DTABR (cvAUC 0.827, 95% CI 0.758 - 0.895) or alpha RP (cvAUC 0.814, 95% CI 0.742 – 0.885) preform significantly better (DeLong tests: p=0.009 and p=0.023, respectively). The discriminative capacity of models including DTABR or alpha RP was similar (DeLong tests p=0.3525)

Analogously, for 12-month outcome, compared with the model with known functional outcome predictors (cvAUC 0.794, 95% CI 0.722 - 0.865), both models including DTABR (cvAUC 0.859, 95% CI 0.800 - 0.919) and alpha RP (cvAUC 0.852, 95% CI 0.790 – 0.913) had significantly higher discriminative capacity (DeLong tests: p=0.009 and p=0.015, respectively). As for discharge, the predictive power of models including DTABR or alpha RP was similar (DeLong tests p=0.5482)

Moreover, for both discharge and 12-month unfavourable outcome, NIHSS remains as the only independent predictor together with any of the two qEEG indices.

Finally, visual analysis of EEG background asymmetry was also an independent prognostic marker of poor functional outcome at discharge (cvAUC 0.831, 95% CI 0.762 - 0.900) and 12 months (cvAUC 0.890, 95% CI 0.837 - 0.943) and performed significantly better than the known functional outcome predictors model alone (DeLong test: 0.010 for discharge and 0.001 for 12 months). The discriminative capacity of the model incorporating visual EEG analysis was not significantly different compared with models with either qEEG index (DTABR - DeLong test: 0.767 for discharge and 0.185 for 12 months; alpha RP - DeLong test: 0.190 for discharge and 0.100 for 12 months).

Table 26. Comparison between stroke outcome (mRS≥3) prediction models characteristics at discharge (A) and 12 months (B).

Model	Omnibus Test	Nagelkerkes R^2	Hosmer & Lemeshow test	PAC (%)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	Cross-validated AUC (95% CI)
A. Unfavourable outcome at discharge									
KP[a]	$\chi^2(3)=34.94$; p<0.001	0.294	$\chi^2(8)=4.90$; p=0.768	73.3	85.4	50.0	76.6	64.1	0.752 (0.671 - 0.834)
Alpha RP[b]	$\chi^2(1)=28.5$; P<0.001	0.238	$\chi^2(8)=10.1$; p=0.259	72.8	86.9	46.2	75.4	64.9	0.756 (0.674 - 0.838)
DTABR[b]	$\chi^2(1)=37.3$; P<0.001	0.302	$\chi^2(8)=4.74$; p=0.785	71.5	84.8	46.2	75.0	61.5	0.785 (0.710 - 0.860)
KP[a] + alpha RP[b]	$\chi^2(4)=50.79$ p<0.001	0.406	$\chi^2(8)=5.07$; p=0.751	76.7	85.4	60.0	80.4	68.2	0.814 (0.742 - 0.885)
KP[a] + DTABR[b]	$\chi^2(4)=3.73$ p<0.001	0.426	$\chi^2(8)=4.44$; p=0.816	78.1	87.5	60.0	80.7	71.4	0.827 (0.758 - 0.895)
KP[a] + visually analysed EEG background asymmetry	$\chi^2(4)=59.25$ p<0.001	0.461	$\chi^2(8)=3.67$; p=0.885	76.7	81.3	68.0	82.9	65.4	0.831 (0.762 - 0.900)
KP[a] + visually analysed EEG background slowing[b]	$\chi^2(4)=46.61$ p<0.001	0.378	$\chi^2(8)=5.01$; p=0.756	74.7	82.3	60	79.8	63.8	0.787 (0.713 - 0.861)
B. Unfavourable outcome at 12 months									
KP[a]	$\chi^2(3)=52.15$; p<0.001	0.403	$\chi^2(8)=5.20$; p=0.736	71.0	70.3	71.8	72.2	69.8	0.794 (0.722 - 0.865)
Alpha RP[b]	$\chi^2(1)=36.42$; p<0.001	0.287	$\chi^2(8)=15.6$; p=0.048	68.0	70.1	65.8	68.4	67.6	0.768 (0.692 - 0.844)
DTABR[b]	$\chi^2(1)=40.52$; p<0.001	0.316	$\chi^2(8)=9.98$; p=0.266	70.7	76.6	64.4	69.4	72.3	0.774 (0.697 - 0.850)
KP[a] + alpha RP[b]	$\chi^2(4)=73.48$ p<0.001	0.530	$\chi^2(8)=6.61$; p=0.579	77.2	75.7	78.9	78.9	75.6	0.852 (0.790 - 0.913)
B. Unfavourable outcome at 12 months									

KP[a] + DTABR[b]	$\chi^2(4)=73.15$; p<0.001	0.528	$\chi^2(8)=8.78$; p=0.361	77,2	79,7	74,6	76.6	77.9	0.859 (0.800 - 0.919)
KP[a] + visually analysed EEG background asymmetry	$\chi^2(4)=93.52$; p<0.001	0.634	$\chi^2(8)=4.38$; p=0.82	84.8	81.1	88.7	88,2	81,8	0.890 (0.837 - 0.943)
KP[a] + visually analysed EEG background slowing[b]	$\chi^2(4)=83.169$ p<0.001	0.582	$\chi^2(8)=5.96$; p=0.652	82.8	78.4	87.3	84.1	79.5	0.866 (0.808 - 0.924)

Legend to table 26: KP - known post-stroke outcome predictors (age, admission NIHSS, 1st CT ASPECTS score); RP - relative power; DTABR - delta-theta to alpha-beta ratio; a - age and ASPECTS are non-significant variables in the model; b - 1st EEG (0 to 72 hours); PAC - Percentage accurately classified; SEN - sensitivity; SPE - specificity; PPV - positive predictive value; NPV - negative predictive value; AUC - area under the ROC curve; CI – confidence interval.

3.2.2.1 Cutoff values for alpha relative power in the first EEG

Table 27 shows the sensitivity and specificity values for alpha RP obtained from the first EEG, for predicting unfavourable outcome. This neurophysiological variable, in isolation, predicts unfavourable outcome with an area under the ROC curve of 0.750 (95% CI 0.669-0.832) at discharge and 0.769 (95%CI 0.695-0.844) at 12 months. For both discharge and 12-month outcomes, an alpha RP lower than 10% on an EEG performed in the first 72h post-stroke shows high specificity to predict unfavourable outcome (87-89%), despite low sensitivity (37-46%). Alpha RP below 20% have higher sensitivity to predict patients with unfavourable outcome (86 and 90%, respectively) albeit low specificity.

Table 27. Sensitivity and specificity of different Ln D1 alpha RP values for predicting unfavourable outcome.

Death or functional dependency at discharge (mRS≥3)		
1st EEG (0 – 72 hours)	Sensitivity	Specificity
Ln alpha RP ≤ -2.3 (alpha RP ≤ 10%)	37-46%	87-89%
Ln alpha RP ≤ -1.9 (alpha RP ≤ 15%)	66-70%	67-71%
Ln alpha RP ≤ - 1.6 (alpha RP ≤ 20%)	86%	52-54%
Death or functional dependency at 12-month post-stroke (mRS≥3)		
Ln alpha RP ≤ -2.3 (alpha RP≤10%)	46-53%	86-89%
Ln alpha RP ≤ -1.9 (alpha RP ≤15%)	71-77%	53-66%
Ln alpha RP ≤ -1.6 (alpha RP ≤20%)	90%	44-45%

Legend to table 27: Ln - natural logarithm; RP - relative power

4. DISCUSSION

To the best of our knowledge, this is the largest study evaluating quantitative EEG parameters for prediction of post-stroke functional outcome. In a consecutively selected, well defined, acute anterior circulation ischaemic stroke cohort, the predictive accuracy of qEEG measures was examined while controlling for clinical and imaging variables, which are available and easily determined in clinical practice in a stroke unit.

In this study, comparing absolute and relative frequency band power indices, symmetry measures and dynamic time changes, we have shown that most qEEG indices previously reported in the literature are independent prognostic markers for poor functional outcome. Additionally, DTABR and alpha RP are some of the most accurate neurophysiological markers for outcome prediction, both at discharge and 12 months after stroke. Lower alpha RP, higher DTABR and higher NIHSS scores were sufficient to predict poor functional outcome, rendering age and ASPECTs scores non-significant in our models. Furthermore, these qEEG indices seem to provide additional prognostic information to already known clinical and imaging-related predictors, and with similar performance to previously reported visual EEG analysis of background asymmetry. Finally, we report that alpha RP below 10% is highly specific for a poor functional outcome at both timelines.

Negative correlation between alpha activity and stroke outcome is in accordance with several previous studies[285,293,296,297,305,306]. Alpha frequencies are thought to derive from cortical layers IV and V, whereas slower delta or theta frequencies are generated by the thalamus and cortical layers II-VI[307]. Therefore, it is not surprising that alpha activity disturbances reflect direct cortical injury[308]. Furthermore, the change in faster frequencies, such as alpha, is thought to precede the increase in slower frequencies, as shown in patients undergoing carotid endarterectomy with continuous EEG and cerebral blood flow measurements[66]. In 47 patients with unilateral cerebral infarction, relative alpha frequency positively correlated

with regional cerebral blood flow and oxygen metabolism, as measured by positron emission tomography[52]. The same variable has been positively correlated with cognitive outcome (in a functional assessment scale), as well as with improvement in post-stroke aphasia[305,306]. This assessment might even be extended to critical care ventilated patients, where a decrease in faster frequency activity has been associated with a drop in cerebral perfusion pressure[309]. In patients presenting with subarachnoid haemorrhage, relative alpha power was able to predict the development of delayed cerebral ischaemia[310]. Moreover, alpha activity may rapidly increase after successful reperfusion due to rt-PA administration in acute stroke[311]. In a previous study we have shown that, in visual EEG analysis, the variables most strongly associated with outcome were background activity slowing and background activity asymmetry[304]. On visual analysis, background slowing is usually related to a decrease in alpha frequency or absent alpha activity. Therefore, the qEEG findings are in accordance with the visual analysis.

Other neurophysiological variables (DTABR, DAR, delta RP), also strongly and independently associated with outcome, incorporate lower frequencies, such as delta power. Delta oscillations usually emerge and have higher voltage in the core lesion of ischaemic stroke patients[60]. They may be more predominant in the affected hemisphere, but their presence in the unaffected side, as measured by EEG and magnetoencephalography, has been described as an important prognostic factor[296,312,313]. In our sample, the DTABR was the qEEG index that was associated with higher AUC to predict short and long–term poor prognosis after stroke. DTABR correlates negatively with cerebral perfusion accessed by Position Emission Tomography in stroke patients[52] and has been shown to be very sensitive and specific for discriminating between cerebral ischemia and controls[314] and to be an independent prognostic factor for short-term disability after lacunar stroke[315]. Sub-acute DTABR also predicted 6 months-disability in an unselected population of stroke patients[299].

Our data reinforces the importance of this qEEG parameter as a strong predictor for short and long term functional stroke outcome, when obtained as early as the first 72h after stroke. To the best of our knowledge, no previous study directly compared the accuracy of alpha RP and DTABR as functional stroke outcome predictors. Our data suggests that they are not significantly different. In our study, we focused on reporting the predictive value of alpha RP for several reasons. Firstly, our data has shown that models with DTABR and alpha RP have similar discriminative capacities. DTABR, besides requiring a more specific computation, incorporates the delta frequency band that is more frequently interfered by artifacts such as blinking, slow shifts or sudation. In the clinical setting, where continuous EEG signal might not be submitted to the strict scrutiny for artifacts, as in this research, its value may not be comparable. Overall, alpha RP seems a preferable neurophysiological marker as it analyses the brain oscillatory activity with higher signal to noise ratio on scalp EEG. Furthermore, some EEG patterns, such as Rapid Attenuation Without Delta, may not be detected by analysing delta frequencies, and may be present in large occlusive infarcts with poor outcome[316].

In other studies, qEEG brain symmetry parameters have been associated with functional outcome[62,284,298,299,317]. In our study, however, qEEG symmetry indices were not significant on multivariate analysis. We used an average montage before performing spectral analysis, which may reduce asymmetries between oscillatory brain activities.

We have also shown that the discriminative capacity of EEG characteristics obtained from visual EEG analysis is similar to qEEG indices. This is an important finding, as visual EEG analysis is cumbersome and dependent on trained neurophysiologists. In contrast, qEEG indices can be readily and easily available in a stroke unit and can be interpreted by all health personnel.

One important finding in our study is the weaker effect of CT imaging lesion size (ASPECTS), obtained from the first CT scan after stroke, when compared to DTABR and alpha RP in outcome prediction. To date, no previous study has compared ASPECTS with qEEG parameters in outcome prediction. Although neuroimaging with CT adds invaluable diagnostic information for stroke patients, this technique has several limitations regarding lesion volume determination especially in the acute/hyperacute phase[279]. During this period, qEEG data may be more reliable and easy to monitor, especially in intensive care settings.

Several limitations of this work are common to other qEEG studies. Effective identification and exclusion of EEG artifacts may be a challenge, such as muscle artifacts interfering with faster activities, or eye movements with delta activity. In our study, besides using an automatic method for artifact removal, an additional visual rejection was done. This may render the results less applicable to qEEG measures in intensive care units, when depending solely upon automatic artifact removal. These results were also obtained from 62-channel EEG that are not routine for EEG monitoring. Further studies are necessary to validate these data.

In conclusion, in a large, well defined cohort of acute anterior ischaemic stroke patients, we found that the alpha RP or DTABR are qEEG variables that contribute significantly for post-stroke outcome prediction, at discharge and 12 months after stroke, when controlled for demographic, clinical and imaging variables.

XIII. SUMMARY of PROJECTS MAIN FINDINGS

"I am among those who think that science has great beauty"

Marie Curie

PROJECT 1

Question 1. What is the frequency of electroencephalographic abnormalities in patients with possible TIA and to which clinical/imaging characteristics are they associated?

- Focal slow wave activity was the commonest EEG abnormality in patients with possible TIA, being found in 65% of early exams and was independently associated with age.
- 7.5% of patients with possible TIA had epileptiform activity in the early EEG. Epileptiform activity was significantly associated with consciousness disturbance.

Question 2. What is the percentage of patients with possible TIA having a final diagnosis of epileptic seizure or definitive TIA and which electroencephalographic characteristics differentiate these diagnoses?

- 16.3% of patients with possible TIA had a final diagnosis of an epileptic seizure and 13.3% of definitive TIA.
- The majority (53.8%) of patients with a final diagnosis of epileptic seizures did not have epileptiform activity in the early EEG. However, all patients with epileptiform activity had the diagnosis of an epileptic seizure during the follow-up study.
- In patients with epileptic seizures, focal slow wave activity in the early EEG was more common than epileptiform activity. However, focal slow wave activity in the early EEG did not distinguished between TIA and seizure diagnosis.
- Focal slow wave activity in the EEG one month after the clinical episode was more likely in patients with epileptic seizures than with a TIA (91.7% vs. 45.4%).

PROJECT 2

Question 3. What is the frequency of post-stroke EEG epileptiform activity, both ictal and interictal in observational studies?

- The pooled frequency of post-stroke ictal and interictal epileptiform activity was 7% (95%CI 3%-12%) and 8% (95%CI 4%-13%), respectively.
- The frequency of ictal EEG epileptiform activity did not change with continuous record or clinical setting, while the frequency of interictal EEG epileptiform activity increased with continuous recordings.
- Only 2 studies (11.7%) attained the maximum quality score.
- No study exclusively enrolled patients with ischaemic stroke.
- The available literature does not answer how the frequency of clinical seizures is related to the frequency of electrographic seizures.

PROJECT 3

Question 4. Is the frequency of electrotrographic and clinical seizures different in stroke patients admitted to a Stroke Unit?

- In the first 7 days after an anterior circulation stroke, more than one-fifth of patients (22.7%) with seizures had exclusively electrographic seizures.

PROJECT 4

Question 5. What is the frequency of *epilepsia partialis continua* as a remote stroke complication?

- The frequency of *epilepsia partialis continua* as a remote complication of anterior circulation ischaemic stroke is very low (1.7%).

PROJECT 5 (clinical vignette)

Question 6. Are involuntary movements observed during intravenous alteplase perfusion of cortical origin?

- During intravenous alteplase perfusion, a patient with an acute middle cerebral artery ischaemic stroke developed subtle involuntary movements of the paretic upper limb with cortical origin, as documented neurophysiologically by back-average analysis.

PROJECT 6

Question 7. Is the frequency of seizures and electroencephalographic abnormalities different between stroke patients treated and non-treated with rtPA?

- Patients treated with intravenous alteplase had the same frequency of epileptic manifestations (either clinical or electroencephalographic) as non-treated patients.
- Functional outcome of patients with post-stroke seizures was also not different between groups.

PROJECT 7

Question 8. Are early electroencephalographic abnormalities independent predictors of post-stroke epilepsy?

- Early EEG abnormalities (background activity asymmetry and interictal epileptiform activity) could predict epilepsy in the first year after stroke, independently from age and clinical and imaging infarct severity.

Question 9. Which are the predictors of EEG epileptiform activity in acute ischaemic stroke?

- An early EEG with periodic discharges and a CT scan with islands of preserved cortex within the infarct, independently predicted the occurrence of EEG epileptiform activity during hospitalization for acute stroke.

PROJECT 8

Question 10. Are seizures and early electroencephalographic abnormalities independent predictors of stroke functional and vital outcome?

- Unprovoked seizures (post-stroke epilepsy) were independent predictors of unfavourable outcome and acute symptomatic seizures of vital outcome, 1 year after an anterior circulation ischaemic stroke.
- Early raw EEG abnormalities (background activity slowing and asymmetry) were independent predictors of an anterior circulation ischaemic stroke functional outcome at discharge and 1 year after stroke. Early EEG asymmetry had the highest odds of impacting stroke functional outcome.
- Early EEG suppression was an independent predictor of anterior circulation ischaemic stroke vital outcome.

PROJECT 9

Question 11. Are qEEG abnormalities independent predictors of stroke functional outcome?

- EEG spectral powers in the alpha, beta and delta bands are unfavourable outcome predictors after acute anterior ischaemic stroke.
- Delta-theta to alpha-beta ratio (DTABR) and alpha relative power (RP) obtained within the first 72h post-stroke are good qEEG predictors of post-stroke short and long-term outcome.
- Outcome models that incorporate DTABR or alpha RP are better than models based exclusively on clinical and imaging-related ischaemic stroke severity at hospital admission.

Question 12. Is qEEG superior to visual analysis in the prediction of stroke functional outcome?

Outcome prediction models including variables extracted from visual and quantitative analysis of the EEG showed similar characteristics.

XIV. DISCUSSION

"What we know is a drop, what we don´t know is an ocean"

Isaac Newton

1. GENERAL DISCUSSION

In this work, different electroencephalography technics were used in the clinical workup of patients with possible and definite cerebrovascular disease as tools for the differential diagnosis and for brain functional assessment, concerning not only epileptic seizures and epileptiform activity detection, but also the identification of independent post-stroke epilepsy and stroke (functional and vital) outcome predictors.

A short duration video-EEG protocol supported epileptic seizure diagnosis in 7.5% of patients with possible TIA and identified 22.7% of acute symptomatic seizures in patients with an anterior circulation ischaemic stroke that were exclusively electrographic, and therefore could not otherwise be recognised. It also allowed the conclusion that seizure frequency is not significantly different between intravenous alteplase treated and non-treated patients. The frequency of electrographic seizures (4.6%) and interictal epileptiform activity (11.9%) found in our acute stroke patients cohort was in line with the pool frequency determined, also in this thesis, by systematic review and meta-analysis technics. Furthermore, we were able to overcome some identified limitations of the existing literature by prospectively studying an exclusively ischaemic stroke cohort consecutively submitted to clinical and EEG assessments. This methodology helped to answer how the frequency of clinical seizures is related to the frequency of electrographic seizures, drawing attention to their recognition in a Stroke Unit, the current standard of care for stroke patients.

EEG back-average analysis was also used to document the cortical origin of involuntary movements during intravenous alteplase perfusion in a patient with acute stroke and also *epilepsia partialis continua* as a chronic anterior circulation stroke complication in 1.7% of patients. These results clearly showed the importance of neurophysiology as an adjunctive tool for attentive clinical observation during stroke care.

Furthermore, this work established early post-stroke visual EEG features as independent predictors (adjusted for age and clinical/imaging stroke severity) of epilepsy one year after stroke. Also, an independent association between post-stroke epilepsy and stroke unfavourable outcome was found, setting epilepsy diagnosis as one aspect of clinical importance in stroke patient care and the ultimate role of neurophysiology in its prediction during Stroke Unit hospitalization.

Additionally, early post-stroke visual EEG features and qEEG parameters (from time and frequency domains EEG analysis, respectively) were also recognized as independent

predictors of functional outcome at hospital discharge and at 12 months after stroke. In fact, they were better than a brain CT Scan performed at the emergency department in outcome prediction, adding a further role to the EEG performed in a Stroke Unit.

This research shows the value of EEG in the current paradigm of stroke patient standard care and, as postulated, it expands knowledge both about the role of the EEG as a complementary neurophysiological tool in Neurology and about different aspects of the diagnosis and outcome of Cerebrovascular Diseases and Epilepsy.

1.1. Integrated discussion of research projects

This thesis work started by attempting to answer a clinical question that frequently emerged in our EEG laboratory: is the EEG useful for the diagnosis of possible TIA? In 2012, the majority of EEG requests aiming to help the differential diagnosis of transient neurological symptoms were from patients attending the TIA clinic every weekday. In **Project 1**[318], we determined the frequency of EEG interictal epileptiform activity in patients with possible TIA, setting out the EEG utility as a differential diagnose tool in a TIA outpatient clinic. We found that in the majority of possible TIA cases (92.5%) an early EEG after the clinical event does not distinguish between a TIA and an epileptic seizure and that it supports the clinical diagnosis of an epileptic seizure only in 46.2% of the cases. Nevertheless, we found clinical characteristics of possible TIA significantly associated with the presence of EEG interictal epileptiform activity, namely a transient neurological syndrome with consciousness disturbance. A possible different time evolution of focal slow wave activity between a TIA and an epileptic seizure was also postulated, although with a low statistical power. This project was an exploratory study which emerged from a frequent and important clinical problem, the difficulty of the differential diagnosis of possible TIA, and was prospectively performed in a clinical setting. These are distinctive methodological differences from De Reuck & Van Maele study[50] which looked for EEG findings only in TIA and inhibitory seizure elderly patients. Our study clearly reflects the differential diagnosis difficulty of possible TIA, even when this diagnosis attempt is made by two different expertize neurologists, and the need for other complementary strategies supporting the classification of these undefined events[17]. Although, theoretically, an EEG during the clinical event could be more informative, the transient nature of these events makes the feasibility of this procedure in clinical practice very unlikely. Other increasing EEG sensibility procedures for

detecting epileptiform activity such as acute and brief sleep deprivation can eventually be explored in the clinical practice in the future[3,8]. Our data, although modest, provide a clear message to practising clinicians and increase clinical awareness and scientific interest for this common and clinically significant, although poorly explored, topic in daily Neurology practice.

We moved forward exploring the frequency of epileptiform activity in established cerebrovascular disease. Our systematic review and meta-analysis of observational studies (**Project 2**[319]) documented that the frequency of ictal and interictal epileptiform activity in the EEG after stroke (7%, 95%CI 3%-12% and 8%, 95%CI 4%-13%, respectively) was comparable with previous frequency analysis of clinical seizures[320]. However, these values might have been underestimated due to methodological limitations previously discussed. Furthermore, only 12% of the observational studies reporting the frequency of post-stroke epileptiform activity had high quality standard, clearly showing the need for higher quality studies regarding this subject. Different caveats to the interpretation of clinical data related to post-stroke epileptiform manifestations[27] became evident and increased our motivation for the next studies. Examples of encountered limitations include the accuracy of stroke diagnosis, the prevalence of different types of stroke in a given study population, the different epilepsy and seizure definition in accordance to their time of occurrence after stroke, the follow-up duration time, the sample size, the heterogeneity in study designs, the availability and analysis of CT and MRI scans for diagnosis and follow-up, the accuracy regarding the location and type of primary lesion, the previous diagnosis of epileptic seizures and epilepsy and the availability, the type, the time after stroke, and the duration of the EEG record for detection of epileptiform activity. In fact, the data in large post-stroke seizures studies derives mainly from investigations done during routine clinical practice[27]. EEG is usually performed when the nature of the post-stroke paroxysmal event is uncertain or if consciousness impairment is not fully explained by the structural brain lesion. Moreover, when analysing the frequency of electrographic seizures and interictal epileptiform activity after stroke it was not possible to include studies enrolling exclusively participants with ischaemic stroke. We realized that although it is the most frequent stroke type, it was a poorly explored clinical model in this context. Our Project 2 strongly argued for the need for better quality prospective studies to understand how the frequency of clinical seizures relates to the frequency of electrographic ones and to evaluate if the presence of interictal epileptiform activity could be an independent predictor of clinical seizures. Furthermore, we did not find

high quality evidence to strongly recommend the use of continuous versus spot EEG in patients with cerebrovascular disorders not admitted to an intensive care unit.

The limitations of the studies recognised in the systematic review and meta-analysis reinforced the value of our study design to evaluate the potential role of EEG in stroke patients concerning both the detection of interictal epileptiform activity and epileptic seizures after stroke. In **Project 3**[270], we found that in the first 7 days after stroke more than one-fifth of patients with seizures had exclusively electrographic seizures and more than one fourth of acute symptomatic seizure patients having a vascular epilepsy diagnosis in 1-year time period would not have been identified without the EEG protocol that was used. Our results reinforce the concept that the exclusively clinical definition of a seizure[146] can be insufficient both in clinical and research settings[321]. It is important to say that our study was performed in a Stroke Unit, where (it is recommended that all stroke patients should be treated[72]) patients receive organised inpatient care from a devoted and specialised multidisciplinary team. So, even with the best clinical care available, an important fraction of post-stroke seizures was not diagnosed, further increasing the value of EEG in this context. Additionally, the meaning of electroencephalographic evaluation was reinforced in the follow up of our cohort (**Project 4**[322]), as one year after the cerebrovascular event, 1.7% of patients had clinical and neurophysiological criteria for the diagnosis of *epilepsia partialis continua.* The place of the EEG in the diagnosis of the clinical presentation subtlety of cortical hypersynchronisation manifestations was also shown in our clinical vignette (**Project 5**[33]). During intravenous alteplase perfusion, one of our cohort patients developed subtle involuntary movements of the paretic upper limb, with proven cortical origin by the neurophysiological evaluation, suggesting the existence of a hypersynchronisation cortical area. These results (of projects 3, 4 and 5) show the importance of EEG in the diagnosis of epileptic manifestations, since clinical evaluation cannot always make the diagnosis by itself. One could argue that this inference is not a new concept in the epileptology community. However, this statement has been proven only for critically ill stroke patients, more frequently admitted to an intensive care unit and with clinical indication for a neurophysiological recording[75], mainly given the suspicion (or during treatment) of non-convulsive *status epilepticus*. The originality of our work was to prospectively ascertain the veracity of this assumption in a prospective and consecutive ischaemic stroke cohort admitted to a Stroke Unit of a Neurology Department. Although, in our study, the percentage of patients with exclusively electrographic seizures is apparently different from the study of

Claassen et al.[75] (22.7% vs. 92%), these data cannot be compared due to a different methodological workup, including study design, population characteristics and the neurophysiological method performed in each study. Furthermore, another innovative aspect was to document the importance of the EEG for the recognition of epileptic manifestations not only in the acute stroke phase but also 1 year after stroke with EEG back-average analysis allowing the recognition of *epilepsia partialis continua* patients. Our studies increase awareness of and scientific interest in the EEG as a tool for the identification of epileptic manifestations in stroke patients. In addition, even if some of these manifestations were rare, the global prevalence of cerebrovascular diseases make these events important not only in terms of frequency but also because different epileptiform manifestations (such as epileptic seizures and *status epilepticus*) have been associated with an unfavourable prognosis after stroke [44,45,79–82].

Previous studies[28,29] and our clinical vignette (Project 5[33]) prompt the hypothesis that intravenous alteplase treatment could be associated with a different frequency of epileptic manifestations after stroke. This hypothesis was also tested in this thesis (**Project 6**[271]). Intravenous alteplase treatment is recommended for acute stroke[72] and the hypothesis that this treatment could affect acute symptomatic seizures or post-stroke epilepsy frequency was thought to have a great clinical impact. However, in our study, intravenous alteplase was not associated with an increased risk of clinical seizures or electroencephalographic epileptiform activity. The fact that (alteplase) treated and non-treated patients had a similar clinical and imaging severity of the infarct (two important risk factors for post-stroke seizures[140,141]) might explain why post-stroke seizures during or after hospitalization were not significantly different between the two groups of patients and justify why our results are more reassuring than previous ones[28,29]. Moreover, the occurrence of seizures in intravenous alteplase treated patients has been associated with different stroke functional outcomes[28,32,34,35,172]. This project also showed that the percentage of patients with seizures and an unfavourable outcome after 12 months was similar between treatment groups. Likewise, this was an important observation, also driving our subsequent work on the effect of seizures in stroke outcome (Project 8[274]).

In this study, another interesting finding was that the diffuse slowing of background activity in the 1st EEG was significantly more frequent in treated patients. However, this difference was no longer significant at discharge nor 12 months after stroke. This result can be partially explained by the fact that treated patients had more severe strokes at admission than those

non-treated. However, this should not be the only factor because alteplase treatment took place at the emergency department and the first EEG was performed the next day at Stroke Unit, when NIHSS score was not significantly different between treated and non-treated patients. Therefore, we showed that diffuse slowing (an EEG sign of cerebral dysfunction) recorded in the first 72 hours after stroke was temporary and reversible, and as such, a possible neurophysiological correlate of the already described "stunned brain" syndrome[166,167].

Pitkänen and Engel[323] defined a biomarker for epilepsy as “an objectively measurable characteristic of a biological process that reliably identifies the development, presence, severity, progression, or localization of an epileptogenic abnormality”. Because an EEG identifies biomarkers of epileptogenesis and ictogenesis[4,5,324], the role of an early EEG in the prediction of post-stroke epilepsy and in the recognition of patients who will have epileptiform activity in the EEG in the Stroke Unit (as described in Project 3), seemed a very pertinent clinical question. In **Project 7**[325], neurophysiological independent risk factors for epilepsy in the year after an anterior circulation ischaemic stroke were added to previously known ones (namely clinical and imaging stroke severity[140,141]), helping to identify patients with an increased risk for post-stroke epilepsy. One of these risk factors was the presence, in an early post-stroke EEG, of interictal epileptiform activity. Notwithstanding, one question should be asked: why do patients with an acute stroke have interictal epileptiform activity? Does it mean that epileptogenesis has already started? Epileptogenesis refers to the development and extension of tissue capable of generating spontaneous seizures, resulting in the development of an epileptic disorder or progression after the disorder is established[326]. In our study patients with a previous stroke plus a mRS >1 and also with previous seizures were excluded. However, the hypothesis that previous lesions, although minor or asymptomatic, may have a relevant role in the epileptogenic process (starting years before), cannot be excluded in our study. In fact, different levels of evidence support this hypothesis. First, earlier studies[230,327] (and also Project 7) showed that the occurrence of a previous acute symptomatic seizure is a risk factor for an unprovoked seizure, probably reflecting that there is an individual predisposition for seizures. Indeed, not only injury severity, location and type of pathological changes but also genetic factors and pre-injury and post-injury exposure to non-genetic factors (i.e., the exposome) can divide patients with ischaemic stroke into different endophenotypes with a variable risk for epileptogenesis[27]. Second, different studies have shown that previous vascular lesions including leukoaraiosis can be associated with a

higher risk of seizures. In addition to the primary ischaemic injury, existing difficult-to-detect microscale changes in blood vessels and white matter present as epileptogenic pathologies[27]. Maxwell et al.[156] showed that radiological cerebrovascular disease including signs of both large vessel and small vessel disease (periventricular or subcortical white matter lesions including leukoaraiosis) is significantly more prevalent in patients with late onset epilepsy. Furthermore, Gasparini and colleagues[328] studying patients with epilepsy with or without a clinically identified stroke event, but for whom the cause of epileptogenesis was probably vascular, showed that those with leukoaraiosis frequently displayed clinical and EEG signs suggesting temporal lobe epilepsy. Third, data from both animal models and patients with different types of brain injury support the proposal that epileptogenesis and often subclinical epilepsy can start immediately after brain injury without any appreciable latent period[147]. Finally, seizures or epilepsy heralding stroke have been documented[152,329], suggesting that epileptogenesis can begin before stroke.

In Project 7, background activity asymmetry could also predict epilepsy in the first year after stroke, independently from clinical and imaging infarct severity. Because our subsequent work (Project 8) also disclosed that background activity asymmetry was superior to ASPECTS in the prediction of functional outcome one year after stroke, this variable seems to reflect the real extent of the neurophysiological severity of the infarct.

Project 7 was also original in finding neurophysiological and imaging features that independently predicted the occurrence of EEG epileptiform activity during hospitalization for acute stroke. The presence of periodic discharges in an early EEG after stroke and the presence of islands of preserved cortex within the infarct, can help to identify patients with an anterior circulation ischaemic stroke who will need a more extensive or repetitive neurophysiological assessment in the Stroke Unit, including those patients with exclusively electrographic seizures, which corresponds to 1/5 of patients with acute symptomatic seizures, as found in Project 3. Although current guidelines for the treatment of post-stroke seizures[148] recommend that isolated acute symptomatic seizures should not be treated with antiepileptic drugs, there are other reasons why their recognition is important. As also showed in this project, acute symptomatic seizures were independent risk factors for epilepsy in the year after stroke and some previous studies have shown that they might have an impact on stroke, vital and functional, outcome[44,45]. A more personalized medical approach to these patients, aimed at early recognition of unprovoked seizures or counselling about seizure-provoking factors (such as sleep deprivation) could be considered and individually weighted.

In **Project 8**[274], the influence of seizures and early EEG abnormalities in patients outcome, both at discharge and 12 months after stroke, was evaluated controlling for age and clinical/imaging severity of the infarct. Although previously suggested by the literature[44,45,64,79,80,85–88], their independency from other important stroke outcome predictors was not established. We thought that, if they had such a value, the importance of their recognition will be reinforced, adding greater clinical meaning to our previous projects (Project 2, 3, 4, 5 and 7) and to this thesis. As a matter of fact, not only were acute symptomatic seizures and early EEG suppression independent predictors of vital outcome but also post-stroke epilepsy and early EEG asymmetry were independent predictors of functional outcome of patients one year after stroke. Moreover, post-stroke seizures and early EEG abnormalities were better than the CT scan performed at the emergency department in this outcome prediction, adding another value to EEG in the Stroke Unit.

The hypothesis behind **Project 9** was also that from EEG analysis, namely quantitative EEG analysis in this particular project, indexes could be extracted that will prove to be independent stroke outcome predictors. In a world increasingly grounded on automatic and computer-based big data analysis, using EEG outcome variables that are wholly dependent on human long-trained expert visual interpretation could also be a limitation of our work, even in a global internet age. It was possible to conclude that delta-theta to alpha-beta ratio and alpha relative power obtained within the first 72h post-stroke were good qEEG predictors of outcome and superior to ASPECTS in predicting unfavourable outcome of an acute middle cerebral artery infarct.
Another important aspect of this EEG quantitative analysis (Project 9) was the observation that outcome prediction models including variables extracted from visual and quantitative analysis of the EEG showed similar characteristics. This ultimate finding of our project sequence can be interpreted as a validation of EEG visual analysis, giving robustness to previous findings of our research.

1.2. Integrated discussion of neurophysiological methodology

The EEG is an exam that can include different technical procedures to meet the needs of the clinical problem[7]. In this thesis, we used multi-channel and high sampling rate EEG, with synchronised video recording and supplemental surface EMG, ECG and EOG channels. This methodological option allowed us to increase spatial resolution of this neurophysiological

technique, to perform back-average and quantitative EEG analysis and to make the clinical correlation of recorded neurophysiological events. Furthermore, prospective and systematic use of standardized international nomenclature and classification systems[212], recommended for multicentre research on EEG patterns in patients with acute neurological disease[248] was implemented. This procedure has several advantages such as an increase in inter-rater reliability[248,249] and quality assurance[330] and an easier building of research data bases[330]. Furthermore, it follows common neurological and clinical practice terms understandable to other physicians not specialized in EEG[331]. For all these reasons, the reproducibility of our results in future studies and a possible multicentre collaboration is facilitated.

However, there are some limitations in the neurophysiological workup used in this study. The serial and non-continuous nature of the EEG record might be considered a constraint. Interest in and enthusiasm for continuous EEG monitoring of critical neurological patients has increased, a fact that is evident in the literature and in different intensive care departments[332,333]. One of the present indications for its use is the detection of seizures and non-convulsive *status epilepticus* in patients with a supratentorial lesion and consciousness disturbance[332]. One of the arguments for its preferential use is the observation that seizures, mostly non-convulsive, are frequent in patients admitted to intensive care units[75]. This non-convulsive nature means that they will not be diagnosed without an EEG record. However, neither the optimal duration nor when a continuous recorded should be started for more accurate electrographic seizure detection has been completely defined as yet. Furthermore, the clinical evidence favouring a continuous EEG versus a short duration EEG in detecting seizures is in fact limited[76], especially in patients with ischaemic stroke admitted to non-intensive care profile services (**Appendices F and G**) and its cost-benefit is not determined[257]. Continuous EEG requires considerable resources including time, specialized physicians and technicians[333], and is not accessible at all centres, which limits its use in several Stroke Units. In patients admitted to non-intensive care profile departments, there is no robust evidence of continuous EEG superiority versus one or several short duration EEG records. In the recent consensus about continuous EEG[332] it is not clear what is the best EEG technique for functional assessment of the brain, including epileptiform activity detection, in non-sedated conscious patients admitted to non-intensive care profile departments. In this work, early neurophysiological markers of an increased risk of EEG epileptiform activity during hospitalization were found in a single and short duration EEG. This result might guide

the need for a more prolonged study (serial or even continuous) only in some patients. In fact, studies about the performance of one or more short duration records for EEG epileptiform activity detection, like ours, have great clinical impact and the search for EEG markers, suggesting the need for a more prolonged or frequent record, a current trend of electroencephalography research[255,256,272,273,334]. An intensive care unit study with continuous EEG showed that 89% of seizures occurred within 72 h after an ischaemic or haemorrhage cerebral lesion[252] and for that reason all of our stroke patients performed the first EEG within this time window. Besides this, the majority of seizures in critically ill patients in Claassen et al.[75] study occurred in the first hour and in Westfall et al.[256] in the first 30 minutes of the EEG monitoring study. Furthermore, Shafi et al.[273] have showed that the absence of epileptiform activity in the first 30 minutes of an EEG record is associated with the absence of seizures in the rest of the continuous monitoring period of at least 18 hours.

The discussion about whether continuous EEG might have identified more electrographic seizures is not equivalent to the discussion on whether continuous EEG might have identified more patients with electrographic seizures. In fact, it is known that electrographic seizures repeat themselves in the absence of treatment[335] and can have a cyclic pattern of repetition[336]. In the rat model of middle cerebral artery occlusion, animals had a mean of 10.6 seizures within 2 h. However, in Pandian et al study[254] a cyclic pattern was only observed in 6.25% of the patients and in our series 2 out of 7 patients had repeated electrographic seizures during serial EEGs.

In our study, EEG was not only used to detect ictal and interictal epileptiform manifestations in different time windows after stroke but also as a tool to identify cerebral dysfunction and, as such, as a predictor of stroke functional outcome. It can be argued that analysis of a 60 minutes EEG might affect stroke outcome prediction in a different way than a continuous neurophysiological record, even admitting the same neurological status of the patient, including conscious state and pharmacological influences. Despite being called continuous EEG record, its interpretation is most frequently intermittent. In the clinical practice, visual analysis of continuous EEG is usually performed in time-limited segments for time saving reasons. Furthermore, EEG has essentially a non-stationary nature (i.e. EEG signal's statistical characteristics change with time)[337]. For that reason, some quantitative EEG technics including FFT analysis computes the discrete Fourier transform of different short EEG segments.

In our work, the decision to perform a serial EEG study instead of a continuous one mainly relied on our technological, human and logistic capacities and was based on factors of daily clinical practice. Continuous EEG in the first week after stroke was thought to be difficult to implement in a neurological department with no intensive care profile. The maintenance of multiple scalp EEG electrodes for such a long-time period is laborious and not easily tolerate by the non-sedated patient. In fact, in the study of Carrera et al. [29], 18% of continuous EEG records with only 10 electrodes were interrupted by patient agitation. Also, a continuous EEG might have been disruptive in the daily routine of a Neurology Department, where patients are carried to other departments and laboratories to complete the stroke diagnostic workup and complementary exams, some of which are incompatible with the presence of silver scalp EEG electrodes like MRI.

1.3. Integrated discussion of study limitations and strengths

Specific study limitations have been discussed in the corresponding project chapter of this thesis. In an integrated approach, one could say that our sample sizes were a limitation for some analysis, as well as the lack of a non-contrast–enhanced acute CT scan, a systematic control CT scan and/or an MRI study during hospitalization. The serial and non-continuous nature of the EEG might also be considered a constraint and was already discussed. However, it is also important to realize that a convenience sample was used and that it was a daily clinical practice-based study, using the possible (although standardized) ancillary assessment. Actually, being a daily clinical practice-based study lends strength to our results in terms of internal value for the clinical practice in our Stroke Unit and EEG Laboratory.

Also, the multidisciplinary constitution, the interdisciplinary involvement and the quality of the working clinical team provide further robustness to our results. Joining together a nationally recognised Stroke Unit and a Reference Center for Epilepsy, was a win-win situation, both for clinical practice and research. However, the generalization of results is unsuitable, as they only should be inferred to similar units and to patients with similar inclusion and exclusion criteria.

Our rational for studying epileptic seizures and epileptiform activity in the 2nd decade of the 21st century was based on the rapid evolution of stroke care in the years before. This rapid evolution also caused a limitation for our study due to the fact that, during the years of this

study, other acute stroke standards of care have emerged, such as endovascular therapy. So, research will continue on this topic in the years to come.

2. CLINICAL IMPLICATIONS

This thesis data allows some clear clinical messages:

2.1. In the TIA Clinic:

Epileptic seizures were the most frequently defined final diagnosis in patients with possible TIA, but the chance of an early EEG reporting interictal epileptiform activity was low (7.5%).

2.2. In patients with an acute anterior circulation ischaemic stroke, admitted to the Stroke Unit:

Clinical recognition of seizures was underestimated in more than 1/5 of cases. An EEG protocol can be used to increase the accuracy of this diagnosis.

EEG with back-average analysis allowed the diagnosis of *epilepsia partialis continua* one year after an anterior circulation ischaemic stroke and the recognition of the cortical origin of involuntary movements in one patient during rtPA perfusion.

Patients treated and non-treated with intravenous alteplase had the same frequency of epileptic seizures.

An early post-stroke EEG helped to identify patients with a higher risk of post-stroke epilepsy and also an unfavourable stroke outcome, independently from clinical and imaging severity of the infarct.

3. RESEARCH PERSPECTIVES

From this thesis, several other research questions about EEG and seizures in ischaemic cerebrovascular disease emerge and represent potential possibilities of future research.

One type of research problem that deserves to be explored is, undoubtedly, the performance of different EEG methodologies aiming to increase the sensibility for epileptic manifestations diagnosis and also the prognostic power of this neurophysiological technique in cerebrovascular disorders. Other neurophysiological techniques (such as sleep deprived EEG, sleep quantitative EEG or EEG connectivity analysis) should be used to study the value of EEG in the differential diagnosis of transitory neurological symptoms, in post-stroke epilepsy prediction and in stroke prognostication. Furthermore, a research design can be established evaluating the performance and cost-effectiveness of continuous EEG record, in the detection of electrographic seizures and EEG epileptiform activity, compared to a spot or a serial EEG protocol.

On the other hand, other imaging variables deserve analysis as post-stroke seizure predictors. A detail cerebral lesion study namely of haemorrhagic transformation type or severity and of previous vascular lesions / leucoaraiosis association with epileptic seizures occurrence, can be performed. Likewise, analysis of the relation between some Doppler sonography variables, such as collateral flow and vessel recanalization status merits investigation.

In the present study, posterior circulation infarcts or other types of cerebrovascular diseases such as intracerebral haematomas or venous thrombosis were not included. However, the validation of our study in other types of stroke patients will be of clinical interest.

Furthermore, endovascular therapy for acute stroke was recently included in our clinical practice and one (recently published) study[338] found that haemorrhagic transformation following this procedure is associated with a nearly 5 times higher rate of developing post-stroke seizures within 2 years. Therefore, the frequency of post-stroke seizures in patients with haemorrhagic transformation submitted and non-submitted to endovascular treatment deserves to be studied.

The influence of acute antiepileptic drug prescription in post-stroke epilepsy frequency and stroke outcome also merits further studies. Moreover, the post-stroke epilepsy impact on the quality of life of stroke patients is still an unanswered question.

The advantage of including a neurophysiological variable, such as those identified in this thesis work, in the recently developed post-stroke epilepsy prediction model[175], also deserves to be studied.

Additionally, other epileptogenesis biomarkers (besides those analysed in this thesis) should be studied in the acute cerebrovascular disease clinical model, as they may be clinically valuable. These biomarkers include electrophysiological ones, such as high frequency oscillations and microseizures[5], imaging biomarkers derived from PET, SPECT and functional MRI[5] and genetic biomarkers of brain vulnerability to acquired epilepsy after insult[324]. As a matter of fact, several genetic variants, specifically involved in GABAergic neurotransmission, have been linked to the modulation of seizure threshold after injury [324] and deserves to be studied in post-stroke patients in a translational collaborative study. Also, the study of epigenetic changes in stroke patients seems to be a new opportunity for the comprehension of the epileptogenesis process. Different epigenetic mechanisms have been already implicated in epilepsy[339,340] and have also started to emerge as important players in stroke-induced endogenous brain recovery events such as angiogenesis, neurogenesis, oligodendrogenesis, synaptogenesis and axonal outgrowth[341]. Nevertheless, microRNAs are the leading epigenetic biomarker candidates for the early detection of epilepsy due to their differential expression and ready accessibility in blood samples[339]. A new avenue of research in post-stroke epilepsy is also the study of neuroinflammation and microvascular injury biomarkers [324].

Last but not least, multicentric studies should also be encouraged allowing external validation of these study results, power increase of statistical analysis and fruitful inter-peer discussion.

XV. REFERENCES

"Antes do interesse pela escrita, há outro: o interesse pela leitura.
E mal vão as coisas quando só se pensa no primeiro,
se antes não se consolidou o gosto pelo segundo. Sem ler ninguém escreve"
José Saramago

1. Bentes C, Pimentel J, Ferro JM. Epileptic seizures following subcortical infarcts. *Cerebrovasc Dis* 2001; 12: 331–4.
2. Ferro J, Bentes C. Post-Stroke Epilepsy. *Aging health* 2006; 2: 599–609.
3. Martins da Silva A, Bentes C, Atalaia A, et al. *Recomendações para utilização do electroencefalograma (EEG) em Epilepsia: Relatório à Liga Portuguesa Contra a Epilepsia*. 2011.
4. Engel J, Pitkanen A, Loeb JA, et al. Epilepsy biomarkers. *Epilepsia* 2013; 54: 61–69.
5. Staba RJ, Stead M, Worrell GA. Electrophysiological Biomarkers of Epilepsy. *Neurotherapeutics* 2014; 11: 334–346.
6. Berger H. Über das Elektrenkephalogramm des Menschen. *Arch Psychiatr Nervenkr* 1929; 87: 527–570.
7. Fowle AJ, Binnie CD. Uses and abuses of the EEG in epilepsy. *Epilepsia* 2000; 41 Suppl 3: S10–S18.
8. National Institute for Health and Care Excelence (NICE). *Epilepsies : diagnosis and management. Clinical guideline 137*. 2012.
9. WHO. Neurological disorders: a public health approach. *Neurol Disord public Heal challenges* 2006; 41–176.
10. Fisher CM. Transient paralytic attacks of obscure nature: the question of non-convulsive seizure paralysis. *Can J Neurol Sci* 1978; 5: 267–273.
11. Lee H, Lerner A. Transient inhibitory seizures mimicking crescendo TIAs. *Neurology* 1990; 40: 165–6.
12. Kaplan PW. Focal seizures resembling transient ischemic attacks due to subclinical ischemia. *Cerebrovasc Dis* 1993; 3: 241–243.
13. Primavera A, Giberti L, Cocito L. Focal inhibitory seizures as the presenting sign of ischemic cerebrovascular disease. *Ital J Neurol Sci* 1993; 14: 381–384.
14. Fisher CM. Concerning recurrent transient cerebral ischemic attacks. *Can Med Assoc J* 1962; 86: 1091–9.
15. Muraga K, Suda S, Nagayama H, et al. Limb-shaking TIA: Cortical myoclonus associated with ICA stenosis. *Neurology* 2016; 86: 307–9.
16. Carreño M. Recognition of Nonepileptic Events. *Semin Neurol* 2008; 28: 297–304.
17. Dolmans LS, Rutten FH, EL Bartelink M-L, et al. Serum biomarkers for the early diagnosis of TIA: The MIND-TIA study protocol. *BMC Neurol* 2015; 15: 119.
18. De Reuck J, Van Maele G. Transient Ischemic Attacks and Inhibitory Seizures in Elderly Patients. *Eur Neurol* 2009; 62: 344–348.
19. Hauser WA, Annegers JF, Kurland LT. Incidence of Epilepsy and Unprovoked Seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993; 34: 453–458.
20. Paradowski B, Zagrajek MM. Epilepsy in middle-aged and elderly people : a three-year observation. *Epileptic Disord* 2005; 7: 91–95.
21. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. *Stroke* 2004; 35: 1769–1775.
22. Bladin CF, Alexandrov A V, Bellavance A, et al. Seizures after stroke: a prospective multicenter study. *Arch Neurol* 2000; 57: 1617–1622.
23. Menon B, Shorvon SD. Ischaemic stroke in adults and epilepsy. *Epilepsy Res* 2009; 87: 1–11.
24. Jungehulsing GJ, Heuschmann PU, Holtkamp M, et al. Incidence and predictors of post-stroke epilepsy. *Acta Neurol Scand* 2013; 127: 427–430.
25. Graham NSN, Crichton S, Koutroumanidis M, et al. Incidence and associations of

poststroke epilepsy. The prospective South London stroke register. *Stroke* 2013; 44: 605–611.
26. Zhang C, Wang X, Wang Y, et al. Risk factors for post-stroke seizures: A systematic review and meta-analysis. *Epilepsy Res* 2014; 108: 1806–1816.
27. Pitkänen A, Roivainen R, Lukasiuk K. Development of epilepsy after ischaemic stroke. *Lancet Neurol* 2015; 15: 185–197.
28. Alvarez V, Rossetti AO, Papavasileiou V, et al. Acute seizures in acute ischemic stroke: Does thrombolysis have a role to play? *J Neurol* 2013; 260: 55–61.
29. Carrera E, Michel P, Despland P, et al. Continuous assessment of electrical epileptic activity in acute stroke. *Neurology* 2006; 67: 99–104.
30. Hafeez F, Razzaq M, Levine R, et al. Reperfusion Seizures: A Manifestation of Cerebral Reperfusion Injury After Administration of Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke. *J Stroke Cerebrovasc Dis* 2007; 16: 273–277.
31. Iyer AM, Zurolo E, Boer K, et al. Tissue plasminogen activator and urokinase plasminogen activator in human epileptogenic pathologies. *Neuroscience* 2010; 167: 929–945.
32. Rodan LH, Aviv RI, Sahlas DJ, et al. Seizures during stroke thrombolysis heralding dramatic neurologic recovery. *Neurology* 2006; 67: 2048–2049.
33. Bentes C, Peralta R, Viana P, et al. Cortical myoclonus during IV thrombolysis for ischemic stroke. *Epilepsy Behav Case Reports* 2014; 2: 186–188.
34. Pillay N, Couillard P, Almekhhlafi M, et al. Seizure incidence in stroke patients treated with thrombolysis. *J Neurol Sci* 2009; 285: S249.
35. Couillard P, Almekhlafi MA, Irvine A, et al. Subacute seizure incidence in thrombolysis-treated ischemic stroke patients. *Neurocrit Care* 2012; 16: 241–245.
36. Jordan K. Emergency EEG and Continuous EEG Monitoring in Acute Ischemic Stroke. *J Clin Neurophysiol* 2004; 21: 341–352.
37. Assenza G, Di Lazzaro V. A useful electroencephalography (EEG) marker of brain plasticity: delta waves. *Neural Regen Res* 2015; 10: 1216–1217.
38. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *atlas Hear Dis stroke* 2004; 15: 50–51.
39. Adams HPJ, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999; 53: 126–131.
40. Knoflach M, Matosevic B, Rucker M, et al. Functional recovery after ischemic stroke - A matter of age. *Neurology* 2012; 78: 279.
41. Vogt G, Laage R, Shuaib A, et al. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: An analysis of the Virtual International Stroke Trials Archive (VISTA) database. *Stroke* 2012; 43: 1266–1272.
42. Barber P, Demchuk A, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000; 355: 1670–1674.
43. Stinear C. Prediction of recovery of motor function after stroke. *The Lancet Neurology* 2010; 9: 1228–1232.
44. Hesdorffer DC, Benn EKT, Cascino GD, et al. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia* 2009; 50: 1102–1108.
45. Huang CW, Saposnik G, Fang J, et al. Influence of seizures on stroke outcomes: A large multicenter study. *Neurology* 2014; 82: 768–776.
46. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the

intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996; 47: 83–89.
47. Oddo M, Carrera E, Claassen J, et al. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med* 2009; 37: 2051–6.
48. Kamel H, Betjemann JP, Navi BB, et al. Diagnostic yield of electroencephalography in the medical and surgical intensive care unit. *Neurocrit Care* 2013; 19: 336–341.
49. Rossini PM, Altamura C, Ferretti A, et al. Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? *Brain* 2004; 127: 99–110.
50. De Reuck J, Van Maele G. Transient ischemic attacks and inhibitory seizures in elderly patients. *Eur Neurol* 2009; 62: 344–8.
51. De Reuck J, Goethals M, Claeys I, et al. EEG findings after a cerebral territorial infarct in patients who develop early- and late-onset seizures. *Eur Neurol* 2006; 55: 209–213.
52. Nagata K, Tagawa K, Hiroi S, et al. Electroencephalographic correlates of blood flow and oxygen metabolism provided by positron emission tomography in patients with cerebral infarction. *Electroencephalogr Clin Neurophysiol* 1989; 72: 16–30.
53. Ingvar DH, Sjolund B, Ardo A. Correlation between dominant EEG frequency, cerebral oxygen uptake and blood flow. *Electroencephalogr Clin Neurophysiol* 1976; 41: 268–276.
54. Tolonen U, Sulg IA. Comparison of quantitative EEG parameters from four different analysis techniques in evaluation of relationships between EEG and CBF in brain infarction. *Electroencephalogr Clin Neurophysiol* 1981; 51: 177–185.
55. Astrup J, Siesjo B, Symon L. Thresholds in Cerebral Ischemia — The Ischemic Penumbra. *Stroke* 1981; 12: 723–725.
56. Sundt T, Sharbrough F, Piepgras D. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy. With results of surgery and hemodynamics of cerebral ischemia. *Mayo Clin Proc* 1981; 56: 533–543.
57. Baron JC. Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications. *Cerebrovasc Dis* 2001; 11 Suppl 1: 2–8.
58. Nuwer MR, Jordan SE, Ahn SS. Evaluation of stroke using EEG frequency analysis and topographic mapping. *Neurology* 1987; 37: 1153–9.
59. Niedermeyer E. Cerebrovascular Disorders and EEG. In: Niedermeyer E, Lopes da Silva F (eds) *Electroencephalography: Basic principles, clinical applications, and related fields*. Lippincott Williams & Wilkins, 2005, pp. 339–362.
60. Murri L, Gori S, Massetani R, et al. Evaluation of acute ischemic stroke using quantitative EEG: a comparison with conventional EEG and CT scan. *NeurophysiolClin* 1998; 28: 249–257.
61. Luu P, Tucker DM, Englander R, et al. Localizing acute stroke-related EEG changes: assessing the effects of spatial undersampling. *J Clin Neurophysiol* 2001; 18: 302–317.
62. van Putten MJAM, Tavy DLJ. Continuous Quantitative EEG Monitoring in Hemispheric Stroke Patients Using the Brain Symmetry Index. *Stroke* 2004; 35: 2489–2492.
63. Jordan K. Regional attenuation without delta (RAWOD): a distinctive early EEG pattern in acute cerebral infarctions (SACI). *Neurology* 1998; 50 (suppl1: A43.
64. Schneider AL, Jordan KG. Regional attenuation without delta (RAWOD): a distinctive EEG pattern that can aid in the diagnosis and management of severe acute ischemic stroke. *Am J Electroneurodiagnostic Technol* 2005; 45: 102–117.

65. Jordan KG. Continuous EEG monitoring in the neuroscience intensive care unit and emergency department. *J Clin Neurophysiol* 1999; 16: 14–39.
66. Sharbrough FW, Messick JM, Sundt TM. Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. *Stroke* 1973; 4: 674–683.
67. Jordan KG. Neurophysiologic monitoring in the neuroscience intensive care unit. *Neurol Clin* 1995; 13: 579–626.
68. Wood JH, Polyzoidis KS, Epstein CM, et al. Quantitative EEG alterations after isovolemic-hemodilutional augmentation of cerebral perfusion in stroke patients. *Neurology* 1984; 34: 764–768.
69. Suzuki A, Yoshioka K, Yasui N. Clinical application of EEG topography in cerebral ischemia: detection of functional reversibility and hemodynamics. *Brain Topogr* 1990; 3: 167–174.
70. Goldstein L, Bertels C, Davis J. Interrater reliability of the NIH stroke scale. *Arch Neurol* 1989; 46: 660–662.
71. Finnigan SP, Rose SE, Walsh M, et al. Correlation of Quantitative EEG in Acute Ischemic Stroke with 30-Day NIHSS Score: Comparison with Diffusion and Perfusion MRI. *Stroke* 2004; 35: 899–903.
72. ESO. Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008. *Cerebrovasc Dis* 2008; 25: 457–507.
73. Claassen J, Hirsch L. Stroke and Subarachnoid Hemorrage. In: Fisch B (ed) *Epilepsy and Intensive Care monitoring, principles and practice*. New York:Demos Medical Publishing, 2010, pp. 339–351.
74. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet (London, England)* 2005; 366: 29–36.
75. Claassen J, Mayer S a, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 2004; 62: 1743–1748.
76. Claassen J, Vespa P. Electrophysiologic Monitoring in Acute Brain Injury. *Neurocrit Care* 2014; 21: 129–147.
77. Pawlak R, Strickland S. Tissue plasminogen activator and seizures : a clot-buster ' s secret life. *J Clin Invest* 2002; 109: 1529–1531.
78. Yepes M, Roussel BD, Ali C, et al. Tissue-type plasminogen activator in the ischemic brain: more than a thrombolytic. *Trends Neurosci* 2009; 32: 48–55.
79. De Reuck J, Claeys I, Martens S, et al. Computed tomographic changes of the brain and clinical outcome of patients with seizures and epilepsy after an ischaemic hemispheric stroke. *Eur J Neurol* 2006; 13: 402–407.
80. Arntz RM, Rutten-Jacobs LCA, Maaijwee NAM, et al. Poststroke Epilepsy Is Associated With a High Mortality After a Stroke at Young Age. *Stroke* 2015; 46: 2309–2311.
81. Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke: report on a hospital-based stroke cohort. *Neurology* 2000; 54: 350–354.
82. Knake S, Rochon J, Fleischer S, et al. Status epilepticus after stroke is associated with increased long-term case fatality. *Epilepsia* 2006; 47: 2020–2026.
83. Waterhouse EJ, Vaughan JK, Barnes TY, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. *Epilepsy Res* 1998; 29: 175–183.
84. Williams PA, Dou P, Dudek FE. Epilepsy and synaptic reorganization in a perinatal rat model of hypoxia-ischemia. *Epilepsia* 2004; 45: 1210–1218.
85. Kayser-Gatchalian MC, Neundörfer B. The prognostic value of EEG in ischaemic

cerebral insults. *Electroencephalogr Clin Neurophysiol* 1980; 49: 608–17.
86. Ahmed I. Predictive value of the electroencephalogram in acute hemispheric lesions. *Clin Electroencephalogr* 1988; 19: 205.
87. Cillessen JP, van Huffelen a C, Kappelle LJ, et al. Electroencephalography improves the prediction of functional outcome in the acute stage of cerebral ischemia. *Stroke* 1994; 25: 1968–72.
88. Burghaus L, Hilker R, Dohmen C, et al. Early electroencephalography in acute ischemic stroke: prediction of a malignant course? *Clin Neurol Neurosurg* 2007; 109: 45–9.
89. Cuspineda E, Machado C, Aubert E, et al. Predicting outcome in acute stroke: a comparison between QEEG and the Canadian Neurological Scale. *Clin Electroencephalogr* 2003; 34: 1–4.
90. Prabhakaran S, Silver AJ, Warrior L, et al. Misdiagnosis of transient ischemic attacks in the emergency room. *Cerebrovasc Dis* 2008; 26: 630–635.
91. Fonseca AC, Canhão P. Diagnostic difficulties in the classification of transient neurological attacks. *Eur J Neurol* 2011; 18: 644–648.
92. Correia M, Fonseca AC, Canhao P. Short-term outcome of patients with possible transient ischemic attacks: a prospective study. *BMC Neurol* 2015; 15: 78.
93. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* 2014; 55: 475–482.
94. Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain*. Boston: Little, Brown and Companyhttps://doi.org/10.1001/jama.1954.03690190092039 (1954).
95. Filevich E, Kühn S, Haggard P. Negative motor phenomena in cortical stimulation: implications for inhibitory control of human action. *Cortex* 2012; 48: 1251–61.
96. Ikeda A, Hirasawa KI, Kinoshita M, et al. Negative motor seizure arising from the negative motor area: Is it ictal apraxia? *Epilepsia* 2009; 50: 2072–2084.
97. Lüders HO, Dinner DS, Morris HH, et al. Cortical electrical stimulation in humans. The negative motor areas. *Adv Neurol* 1995; 67: 115–29.
98. Noachtar S, Lüders HO. Focal akinetic seizures as documented by electroencephalography and video recordings. *Neurology* 1999; 53: 427–9.
99. Abou-Khalil B, Fakhoury T, Jennings M, et al. Inhibitory motor seizures: correlation with centroparietal structural and functional abnormalities. *Acta Neurol Scand* 1995; 91: 103–108.
100. Donovan CA, Chan A, Maxwell S. Focal akinetic seizures as the only clinical manifestation of partial epilepsy. *Seizure* 2007; 16: 542–544.
101. Matsumoto R, Ikeda A, Ohara S, et al. Nonconvulsive focal inhibitory seizure: subdural recording from motor cortex. *Neurology* 2000; 55: 429–431.
102. Kovac S, Diehl B. Atonic phenomena in focal seizures: Nomenclature, clinical findings and pathophysiological concepts. *Seizure* 2012; 21: 561–567.
103. Elger CE, Speckmann EJ. Penicillin-induced epileptic foci in the motor cortex: vertical inhibition. *Electroencephalogr Clin Neurophysiol* 1983; 56: 604–622.
104. Hamilton NG, Matthews T. Aphasia: the sole manifestation of focal status epilepticus. *Neurology* 1979; 29: 745–748.
105. Salanova V, Andermann F, Rasmussen T, et al. Tumoural parietal lobe epilepsy. Clinical manifestations and outcome in 34 patients treated between 1934 and 1988. *Brain* 1995; 118: 1289–1304.
106. Kirshner HS, Hughes T, Fakhoury T, et al. Aphasia secondary to partial status epilepticus of the basal temporal language area. *Neurology* 1995; 45: 1616–1618.
107. Rolak LA, Rutecki P, Ashizawa T, et al. Clinical features of Todd's post-epileptic

paralysis. *J Neurol Neurosurg Psychiatry* 1992; 55: 63–4.
108. Hanoglu L, Ertaş NK, Altunhalka A, et al. Cognitive dysfunction of right hemisphere-like Todd's paralysis after status epilepticus: A case report. *Seizure* 2001; 10: 125–129.
109. Grand'Maison F, Reiher J, Lebel ML, et al. Transient anosognosia for episodic hemiparesis: a singular manifestation of TIAs and epileptic seizures. *Can J Neurol Sci* 1989; 16: 203–205.
110. Erdem S, Saygi S, Ciğer A, et al. Seizures with negative phenomena. *Clin Neurol Neurosurg* 1995; 97: 36–38.
111. Persoon S, Kappelle LJ, Klijn CJM. Limb-shaking transient ischaemic attacks in patients with internal carotid artery occlusion: a case-control study. *Brain* 2010; 133: 915–922.
112. Cocito L, Loeb C. Focal epilepsy as a possible sign of transient subclinical ischemia. *Eur Neurol* 1989; 29: 339–344.
113. Ferracci F, Moretto G, Gentile M, et al. Can seizures be the only manifestation of transient ischemic attacks? A report of four cases. *Neurol Sci* 2000; 21: 303–306.
114. Viswanathan, Anand and Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol* 2011; 70: 871–880.
115. Sakurai K, Tokumaru AM, Nakatsuka T, et al. Imaging spectrum of sporadic cerebral amyloid angiopathy: Multifaceted features of a single pathological condition. *Insights Imaging* 2014; 5: 375–385.
116. Charidimou A, Peeters A, Fox Z, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: Multicentre magnetic resonance imaging cohort study and meta-analysis. *Stroke* 2012; 43: 2324–2330.
117. Smith DB, Hitchcock M, Philpott PJ. Cerebral amyloid angiopathy presenting as transient ischemic attacks. Case report. *J Neurosurg* 1985; 63: 963–964.
118. Greenberg SM, Vonsattel JP, Stakes JW, et al. The clinical spectrum of cerebral amyloid angiopathy: presentations without lobar hemorrhage. *Neurology* 1993; 43: 2073–9.
119. Charidimou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: Recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry* 2012; 83: 124–137.
120. Charidimou A, Baron JC, Werring DJ. Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: Looking beyond TIAs. *Int J Stroke* 2013; 8: 105–108.
121. Paterson RW, Uchino K, Emsley HC, et al. Recurrent stereotyped episodes in cerebral amyloid angiopathy: response to migraine prophylaxis in two patients. *Cerebrovasc Dis Extra* 2013; 3: 81–84.
122. Biffi A, Halpin A, Towfighi A, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology* 2010; 75: 693 LP-698.
123. Charidimou A, Shakeshaft C, Werring DJ. Cerebral microbleeds on magnetic resonance imaging and anticoagulant-associated intracerebral hemorrhage risk. *Front Neurol* 2012; 3: 133.
124. Melo TP, Bogousslavsky J, Regli F, et al. Fatal Hemorrhage during Anticoagulation of Cardioembolic Infarction: Role of Cerebral Amyloid Angiopathy. *Eur Neurol* 1993; 33: 9–12.
125. Mlynash M, Olivot JM, Tong DC, et al. Yield of combined perfusion and diffusion MR imaging in hemispheric TIA. *Neurology* 2009; 72: 1127–1133.
126. Easton JD, Saver JL, Albers GW, et al. Definition and Evaluation of Transient Ischemic Attack: A Scientific Statement for Healthcare Professionals From the

American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardio. *Stroke* 2009; 40: 2276–2293.

127. Albers GW, Caplan LR, Easton JD, et al. Transient Ischemic Attack — Proposal for a New Definition. *N Engl J Med* 2002; 347: 1713–1716.
128. Diehl B, Najm I, Ruggieri P, et al. Postictal diffusion-weighted imaging for the localization of focal epileptic areas in temporal lobe epilepsy. *Epilepsia* 2001; 42: 21–28.
129. Hufnagel a., Weber J, Marks S, et al. Brain diffusion after single seizures. *Epilepsia* 2003; 44: 54—63.
130. Lansberg MG, O'Brien MW, Norbash AM, et al. MRI abnormalities associated with partial status epilepticus. *Neurology* 1999; 52: 1021–7.
131. Rennebaum F, Kassubek J, Pinkhardt E, et al. Status epilepticus: Clinical characteristics and EEG patterns associated with and without MRI diffusion restriction in 69 patients. *Epilepsy Res* 2016; 120: 55–64.
132. Maalouf N, Keyrouz SG. Early appearance of diffusion-weighted hyperintensities in aphasic status epilepticus: A case report. *Neuroradiol J* 2012; 25: 36–39.
133. Lie CH, Seifert M, Poggenborg J, et al. Perfusion computer tomography helps to differentiate seizure and stroke in acute setting. *Clin Neurol Neurosurg* 2011; 113: 925–927.
134. Chiu AH, Phillips TJ, Phatouros CC, et al. CT perfusion in acute stroke calls: A pictorial review and differential diagnoses. *J Med Imaging Radiat Oncol* 2016; 60: 165–171.
135. Hassan AE, Cu SR, Rodriguez GJ, et al. Regional Cerebral Hyperperfusion Associated with Postictal Paresis.
136. Gelfand JM, Wintermark M, Josephson SA. Cerebral perfusion-CT patterns following seizure. *Eur J Neurol* 2010; 17: 594–601.
137. Mathews MS, Smith WS, Wintermark M, et al. Local cortical hypoperfusion imaged with CT perfusion during postictal Todd's paresis. *Neuroradiology* 2008; 50: 397–401.
138. Forsgren L, Beghi E, Õun A, et al. The epidemiology of epilepsy in Europe - A systematic review. *Eur J Neurol* 2005; 12: 245–253.
139. Herman ST. Epilepsy after brain insult. *Neurology* 2002; 59: S21–S26.
140. Leung T, Leung H, Soo YOY, et al. The prognosis of acute symptomatic seizures after ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2017; 88: 86–94.
141. Tanaka T, Ihara M. Post-stroke epilepsy. *Neurochem Int* 2017; 107: 219–228.
142. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 2010; 51: 671–675.
143. Zelano J. Poststroke epilepsy: update and future directions. *Ther Adv Neurol Disord* 2016; 9: 424–435.
144. Silverman IE, Restrepo L, Mathews GC. Poststroke seizures. *Arch Neurol* 2002; 59: 195–201.
145. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* 2008; 49: 8–12.
146. Fisher RS, Boas W van E, Blume W, et al. Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; 46: 470–472.
147. Löscher W, Hirsch LJ, Schmidt D. The enigma of the latent period in the development of symptomatic acquired epilepsy - Traditional view versus new concepts. *Epilepsy Behav* 2015; 52: 78–92.

148. Holtkamp M, Beghi E, Benninger F, et al. European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy. *Eur Stroke J* 2017; 2: 103–115.
149. Zelano J, Larsson D, Kumlien E, et al. Pre-stroke seizures: A nationwide register-based investigation. *Seizure* 2017; 49: 25–29.
150. García-García J, Calleja S, De la Vega V, et al. Heraldic seizure. *Seizure* 2004; 13: 328–330.
151. Elices E, Santamaría J, Arroyo S. Crisis heráldicas como compilación de epilepsia previa. *Neurología* 2001; 16: 83–86.
152. Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. *Lancet* 2004; 363: 1184–1186.
153. Wannamethee SG, Shaper AG, Ebrahim S. HDL-Cholesterol, Total Cholesterol, and the Risk of Stroke in Middle-Aged British Men. *Stroke* 2000; 31(8): 1882–1889.
154. McCarron P, Greenwood R, Elwood P, et al. The incidence and aetiology of stroke in the Caerphilly and Speedwell Collaborative Studies II. *Public Health* 2017; 115: 12–20.
155. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ* 1989; 298: 789–794.
156. Maxwell H, Hanby M, Parkes LM, et al. Prevalence and subtypes of radiological cerebrovascular disease in late-onset isolated seizures and epilepsy. *Clin Neurol Neurosurg* 2013; 115: 591–6.
157. Brigo F, Tezzon F, Nardone R. Late-onset seizures and risk of subsequent stroke: A systematic review. *Epilepsy Behav* 2014; 31: 9–12.
158. Langhorne P, Pollock A, Stroke Unit Trialists' C. Organised inpatient (stroke unit) care for stroke (Review) Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2007; 1–3.
159. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke (Review) Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2013; 2013–2015.
160. Schmitz ML, Simonsen CZ, Hundborg H, et al. Acute ischemic stroke and long-term outcome after thrombolysis: nationwide propensity score-matched follow-up study. *Stroke* 2014; 45: 3070–2.
161. Machado C, Pinho J, Alves JN, et al. Five-Year Outcome in Stroke Patients Submitted to Thrombolysis. *Stroke* 2015; 46: 2312–2314.
162. De Reuck J, Van Maele G. Acute ischemic stroke treatment and the occurrence of seizures. *Clin Neurol Neurosurg* 2010; 112: 328–331.
163. Gravanis I, Tsirka SE. Tissue-type plasminogen activator as a therapeutic target in stroke. *Expert Opin Ther Targets* 2008; 12: 159–70.
164. Ay H, Davis S, Ferro J, et al. *Magnetic Resonance Imaging in Ischemic Stroke*. 1st ed. Springer Science & Business Media, 2006.
165. Ryglewicz D, Baranska-Gieruszczak M, Niedzielska K, et al. EEG and CT findings in poststroke epilepsy. *Acta Neurol Scand* 1990; 81: 488–490.
166. Alexandrov A V., Hall CE, Labiche LA, et al. Ischemic Stunning of the Brain: Early Recanalization Without Immediate Clinical Improvement in Acute Ischemic Stroke. *Stroke* 2004; 35: 449–452.
167. Bang OY, Liebeskind DS, Saver JL, et al. Stunned brain syndrome: serial diffusion perfusion MRI of delayed recovery following revascularisation for acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2010; 82: 27–32.
168. Caplan LR. New therapies for stroke. *Arch Neurol* 1997; 54: 1222–4.
169. Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning.

Physiol Rev 1999; 79: 609–634.
170. Luss H, Schafers M, Neumann J, et al. B iochemical mechanisms of hibernation and stunning in the human heart. *Cardiovasc Res* 2002; 56: 411–421.
171. Goldberg S, Greenspon AJ, Urban PL, et al. Reperfusion arrhythmia: a marker of restoration of antegrade flow during intracoronary thrombolysis for acute myocardial infarction. *Am Heart J* 1983; 105: 26–32.
172. Gensicke H, Seiffge DJ, Polasek AE, et al. Long-term outcome in stroke patients treated with IV thrombolysis. *Neurology* 1990; 80: 919–925.
173. Kim JS, Choi-Kwon S, Kwon SU, et al. Factors affecting the quality of life after ischemic stroke: young versus old patients. *J Clin Neurol* 2005; 1: 59–68.
174. Bladin CF, Alexandrov A V., Bellavance A, et al. Seizures After Stroke. *Arch Neurol* 2000; 57: 1617–1622.
175. Galovic M, Döhler N, Erdélyi-Canavese B, et al. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. *Lancet Neurol* 2018; 17: 117.
176. Jozwiak S, Becker A, Cepeda C, et al. WONOEP appraisal: Development of epilepsy biomarkers-What we can learn from our patients? *Epilepsia* 2017; 58: 951–961.
177. Ní Chróinín D, Asplund K, Åsberg S, et al. Statin therapy and outcome after ischemic stroke: Systematic review and meta-analysis of observational studies and randomized trials. *Stroke* 2013; 44: 448–456.
178. Guo J, Guo J, Li J, et al. Statin treatment reduces the risk of poststroke seizures. *Neurology* 2015; 85: 701–708.
179. Etminan M, Samii A, Brophy JM. Statin use and risk of epilepsy: A nested case-control study. *Neurology* 2010; 75: 1496–1501.
180. Katsiki N, Mikhailidis DP, Nair DR. The effects of antiepileptic drugs on vascular risk factors: A narrative review. *Seizure* 2014; 23: 677–684.
181. Manimekalai K, Visakan B, Salwe KJ, et al. Evaluation of Effect of Antiepileptic Drugs on Serum Lipid Profile among Young Adults with Epilepsy in a Tertiary Care Hospital in Pondicherry. *J Clin Diagn Res* 2014; 8: HC05-9.
182. Vyas M V, Davidson BA, Escalaya L, et al. Antiepileptic drug use for treatment of epilepsy and dyslipidemia: Systematic review. *Epilepsy Res* 2015; 113: 44–67.
183. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol* 2006; 61: 246–255.
184. Stöllberger C, Finsterer J. Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs. *Epilepsy Res* 2016; 126: 98–101.
185. Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. *Epilepsy Behav* 2004; 5: 60–65.
186. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology* 1999; 53: S53-67.
187. Wang JZ, Manav Vyas M V, Saposnik G, et al. Incidence and management of seizures after ischemic stroke. *Neurology* 2017; 1–10.
188. Chung JM. Seizures in the acute stroke setting. *Neurol Res* 2014; 36: 403–406.
189. Naidech AM, Garg RK, Liebling S, et al. Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke* 2009; 40: 3810–3815.
190. Sillanpää M, Gissler M, Schmidt D. Efforts in Epilepsy Prevention in the Last 40 Years. *JAMA Neurol* 2016; 73: 390.
191. Dekkers OM, Egger M, Altman DG, et al. Distinguishing Case Series From Cohort Studies. *Ann Intern Med* 2012; 152: 37–40.
192. Castle J, Mlynash M, Lee K, et al. Agreement Regarding Diagnosis of Transient

Ischemic Attack Fairly Low Among Stroke-Trained Neurologists. *Stroke* 2010; 41: 1367–1370.
193. Ferro JM, Falcao I, Rodrigues G, et al. Diagnosis of Transient Ischemic Attack by the Nonneurologist: A Validation Study. *Stroke* 1996; 27: 2225–2229.
194. Kraaijeveld CL, van Gijn J, Schouten HJ, et al. Interobserver agreement for the diagnosis of transient ischemic attacks. *Stroke* 1984; 15: 723–725.
195. Calanchini PR. Cooperative Study of Hospital Frequency and Character of Transient Ischemic Attacks. *JAMA* 1977; 238: 2029.
196. Jin B, Wu H, Xu J, et al. Analyzing reliability of seizure diagnosis based on semiology. *Epilepsy Behav* 2014; 41C: 197–202.
197. Deacon C, Wiebe S, Blume WT, et al. Seizure identification by clinical description in temporal lobe epilepsy: how accurate are we? *Neurology* 2003; 61: 1686–1689.
198. Beniczky SA, Fogarasi A, Neufeld M, et al. Seizure semiology inferred from clinical descriptions and from video recordings. How accurate are they? *Epilepsy Behav* 2012; 24: 213–215.
199. Larner A. *A Dictionary of Neurological Signs*. 2nd ed. New York, NY: Springer New York. Epub ahead of print 2011. DOI: 10.1007/978-1-4419-7095-4.
200. WHO AC for the NI of ND and B. A Classification and Outline of Cerebrovascular Diseases II. *Stroke* 1975; 6: 564–616.
201. Kidwell CS, Warach S. Acute Ischemic Cerebrovascular Syndrome: Diagnostic Criteria. *Stroke* 2003; 34: 2995–2998.
202. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 2004; 24 Suppl 1: 9–160.
203. Caplan L. Transient global amnesia. In: PJ Vinken PJ, Bruyn GW KH (Eds. . (ed) *Handbook of Clinical Neurology*. Amsterdam: Elsevier, 1985, pp. 205–218.
204. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. *J Neurol Neurosurgery, Psychiatry* 1990; 53: 834–843.
205. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*. 4th ed. Washington D.C.: American Psychiatric Publishing Inc, 2000.
206. D'Ambrosio R, Miller JW. What is an epileptic seizure? Unifying definitions in clinical practice and animal research to develop novel treatments. *Epilepsy Curr* 2010; 10: 61–66.
207. Nuwer M, Comi G, Emerson R, et al. IFCN standards for digital recording of clinical EEG. International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol* 1998; 106: 259–61.
208. Flink R, Pedersen B, Guekht a B, et al. Guidelines for the use of EEG methodology in the diagnosis of epilepsy. International League Against Epilepsy: commission report. Commission on European Affairs: Subcommission on European Guidelines. *Acta Neurol Scand* 2002; 106: 1–7.
209. American Clinical Neurophysiology Society. Guideline 5: Guidelines for Standard Electrode Position Nomenclature. *J Clin Neurophysiol* 2006; 23: 107–110.
210. American Clinical Neurophysiology Society. *Guideline 4: Standards of Practice in Electroencephalography*. 2006.
211. Noachtar S, Binnie C, Ebersole J, et al. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999; 52: 21–41.
212. Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology

Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin Neurophysiol* 2013; 30: 1–27.
213. Samson-Dollfus D, Vernier L, Senant J. [Electroencephalography and normal aging]. *Neurophysiol Clin* 1991; 21: 345–55.
214. York GK, Steinberg DA. Hughlings Jackson's neurological ideas. *Brain* 2011; 134: 3106–3113.
215. Robin JJ, Tolan GD, Arnold JW. Ten year experience with abnormal EEGs in asymptomatic adult males. *Aviat Sp Environ Med* 1978; 49: 732–736.
216. Gregory RP, Oates T, Merry RTG. Electroencephalogram epileptiform abnormalities in candidates for aircrew training. *Electroencephalogr Clin Neurophysiol* 1993; 86: 75–77.
217. Jawad S, Oxley J, Yuen W, et al. The effect of lamotrigine, a novel anticonvulsant, on interictal spikes in patients with epilepsy. *Br J Clin Pharmacol* 1986; 22: 191–193.
218. Pro S, Vicenzini E, Pulitano P, et al. Effects of levetiracetam on generalized discharges monitored with ambulatory EEG in epileptic patients. *Seizure* 2009; 18: 133–138.
219. Rocamora R, Wagner K, Schulze-Bonhage a. Levetiracetam reduces frequency and duration of epileptic activity in patients with refractory primary generalized epilepsy. *Seizure* 2006; 15: 428–33.
220. Milligan N, Dhillon S, Oxley J, et al. Absorption of diazepam from the rectum and its effect on interictal spikes in the EEG. *Epilepsia* 1982; 23: 323–331.
221. Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and management of epilepsy in adults. A national clinical guideline (SIGN 143)*. 2015.
222. Salinsky M, Kanter R, Dasheiff RM. Effectiveness of Multiple EEGs in Supporting the Diagnosis of Epilepsy: An Operational Curve. *Epilepsia* 1987; 28: 331–334.
223. Sundaram M, Hogan T, Hiscock M, et al. Factors affecting interictal spike discharges in adults with epilepsy. *Electroencephalogr Clin Neurophysiol* 1990; 75: 358–360.
224. Vanrumste B, Jones RD, Bones PJ, et al. Slow-wave activity arising from the same area as epileptiform activity in the EEG of paediatric patients with focal epilepsy. *Clin Neurophysiol* 2005; 116: 9–17.
225. Tao JX, Chen XJ, Baldwin M, et al. Interictal regional delta slowing is an EEG marker of epileptic network in temporal lobe epilepsy. *Epilepsia* 2011; 52: 467–476.
226. Di Gennaro G, Quarato PP, Onorati P, et al. Localizing significance of temporal intermittent rhythmic delta activity (TIRDA) in drug-resistant focal epilepsy. *Clin Neurophysiol* 2003; 114: 70–78.
227. Brigo F. Intermittent rhythmic delta activity patterns. *Epilepsy Behav* 2011; 20: 254–256.
228. Meyer JS, Gotoh F, Favale E. Effects of carotid compression on cerebral metabolism and electroencephalogram. *Electroencephalogr Clin Neurophysiol* 1965; 19: 362–376.
229. Easton JD, Saver JL, Albers GW, et al. Definition and Evaluation of Transient Ischemic Attack: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardio. *Stroke* 2009; 40: 2276–2293.
230. Roivainen R, Haapaniemi E, Putaala J, et al. Young adult ischaemic stroke related acute symptomatic and late seizures: risk factors. *Eur J Neurol* 2013; 20: 1247–1255.

231. Rodrigues FB, Bentes C, Duarte GS, et al. *Post-stroke epilepsy frequency/incidence – a protocol of a systematic review and meta-analysis of observational studies. PROSPERO 2015:CRD42015029362*. 2015.
232. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151: W65-94.
233. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44: 2064–2089.
234. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (2009, accessed 13 September 2017).
235. Zou S, Wu X, Zhu B, et al. The pooled incidence of post-stroke seizure in 102 008 patients. *Top Stroke Rehabil* 2015; 22: 460–7.
236. Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: Implications for stroke clinical trials - A literature review and synthesis. *Stroke* 2007; 38: 1091–1096.
237. Rankin J. Cerebral Vascular Accidents in Patients over the Age of 60: II. Prognosis. *Scottish Med J* 1957; 2: 200–215.
238. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; 19: 604–607.
239. Adams H, Bendixen B, Kappelle L, et al. Classification of Subtype of Acute Ischemic Stroke. *Stroke* 1993; 23: 35–41.
240. Ottman R, Barker-Cummings C, Leibson CL, et al. Validation of a brief screening instrument for the ascertainment of epilepsy. *Epilepsia* 2010; 51: 191–7.
241. Alberta Health Services, University of Calgary Medicine Faculty. Training for Aspectshttp://www.aspectsinstroke.com/training-for-aspect (accessed 10 April 2016).
242. Anon. *The SITS Monitoring Study (SITS-MOST) Final Protocol*http://www.acutestroke.org/SM_Protocol/SITS-MOST_final_protocol.pdf (2002).
243. Awada A, Omojola MF, Obeid T. Late epileptic seizures after cerebral infarction. *Acta Neurol Scand* 1999; 99: 265–268.
244. Pohlmann-Eden B, Fatar M, Hennerici M. The preserved cortical island sign is highly predictive of postischemic seizures. *Cerebrovasc Dis* 2001; 12: 282.
245. Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. *Epilepsia* 2013; 54: 28–29.
246. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; 56: 1515–1523.
247. Leitinger M, Beniczky S, Rohracher A, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus - approach to clinical application. *Epilepsy Behav* 2015; 49: 158–163.
248. Gaspard N, Hirsch LJ, LaRoche SM, et al. Interrater agreement for Critical Care EEG Terminology. *Epilepsia* 2014; 55: 1366–1373.
249. Leitinger M, Trinka E, Gardella E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. *Lancet Neurol* 2016; 15: 1054–1062.
250. Chong D, Hirsch L. Which EEG patterns warrant treatment in the critically ill?

Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. *J Clin Neurophysiol* 2005; 22: 79–91.
251. Hartings JAJ, Williams AAJ, Tortella FFC. Occurrence of nonconvulsive seizures, periodic epileptiform discharges, and intermittent rhythmic delta activity in rat focal ischemia. *Exp Neurol* 2003; 179: 139–149.
252. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology* 2003; 60: 1441–1446.
253. Kurtz P, Gaspard N, Wahl AS, et al. Continuous electroencephalography in a surgical intensive care unit. *Intensive Care Med* 2014; 40: 228–234.
254. Pandian JD, Cascino GD, So EL, et al. Digital Video-Electroencephalographic Monitoring in the Neurological-Neurosurgical Intensive Care Unit. *Arch Neurol* 2004; 61: 1090–1094.
255. Swisher CB, Shah D, Sinha SR, et al. Baseline EEG pattern on continuous ICU EEG monitoring and incidence of seizures. *J Clin Neurophysiol* 2015; 32: 147–51.
256. Westover MB, Shafi MM, Bianchi MT, et al. The probability of seizures during EEG monitoring in critically ill adults. *Clin Neurophysiol* 2015; 126: 463–471.
257. Grillo E. Concerns About Utility and Cost-Effectiveness of Continuous Critical-Care EEG. *J Clin Neurophysiol* 2015; 32: 442–443.
258. Meierkord H, Holtkamp M. Non-convulsive status epilepticus in adults: clinical forms and treatment. *Lancet Neurol* 2007; 6: 329–339.
259. Velioglu SK, Ozmenoglu M, Boz C, et al. Status epilepticus after stroke. *Stroke* 2001; 32: 1169–1172.
260. Cockerell OC, Rothwell J, Thompson PD, et al. Clinical and physiological features of epilepsia partialis continua. Cases ascertained in the UK. *Brain* 1996; 119: 393–407.
261. Sinha S, Satishchandra P. Epilepsia Partialis Continua over last 14 years: experience from a tertiary care center from south India. *Epilepsy Res* 2007; 74: 55–9.
262. Caviness JN, Brown P. Myoclonus: Current concepts and recent advances. *Lancet Neurol* 2004; 3: 598–607.
263. Mameniskiene R, Bast T, Bentes C, et al. Clinical course and variability of non-Rasmussen, nonstroke motor and sensory epilepsia partialis continua: A European survey and analysis of 65 cases. *Epilepsia* 2011; 52: 1168–1176.
264. Wilkins DE, Hallett M, Erba G. Primary generalised epileptic myoclonus: a frequent manifestation of minipolymyoclonus of central origin. *J Neurol Neurosurg Psychiatry* 1985; 48: 506–16.
265. Guerrini R. Physiology of epilepsia partialis continua and subcortical mechanisms of status epilepticus. *Epilepsia* 2009; 50 Suppl 1: 7–9.
266. Bansil S, Prakash N, Kaye J, et al. Movement disorders after stroke in adults: a review. *Tremor Other Hyperkinet Mov (N Y)* 2012; 2: 1–7.
267. Mehanna R, Jankovic J. Movement disorders in cerebrovascular disease. *Lancet Neurol* 2013; 12: 597–608.
268. Xu T, Ou S, Liu X, et al. Association between seizures after ischemic stroke and stroke outcome: A systematic review and meta-analysis. *Med open* 2016; 95: e4117.
269. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991; 337: 1521–1526.
270. Bentes C, Martins H, Peralta AR, et al. Post-stroke seizures are clinically underestimated. *J Neurol* 2017; 264: 1978–1985.
271. Bentes C, Martins H, Peralta AR, et al. Epileptic manifestations in stroke patients treated with intravenous alteplase. *Eur J Neurol* 2017; 24: 755–761.

272. Koren J, Herta J, Draschtak S, et al. Prediction of rhythmic and periodic EEG patterns and seizures on continuous EEG with early epileptiform discharges. *Epilepsy Behav* 2015; 49: 286–289.
273. Shafi MM, Westover MB, Cole AJ, et al. Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG. *Neurology* 2012; 79: 1796–1801.
274. Bentes C, Peralta AR, Martins H, et al. Seizures, electroencephalographic abnormalities, and outcome of ischemic stroke patients. *Epilepsia Open* 2017; 2: 441–452.
275. Mecarelli O, Pro S, Randi F, et al. EEG patterns and epileptic seizures in acute phase stroke. *Cerebrovasc Dis* 2011; 31: 191–198.
276. Iijima T, Mies G, Hossmann K. Repeated Negative DC Deflections in Rat Cortex Following Middle Cerebral Artery Occlusion Are Abolished by MK-801 : Effect on Volume of Ischemic Injury Repeated Negative DC Deflections in Rat Cortex Abolished by MK-801 : Effect on Volume of. *J Cereb Blood Flow Metab* 1992; 12: 727–733.
277. De Reuck J, Vonck K, Santens P, et al. Cobalt-55 positron emission tomography in late-onset epileptic seizures after thrombo-embolic middle cerebral artery infarction. *J Neurol Sci* 2000; 181: 13–18.
278. Dachet F, Bagla S, Keren-Aviram G, et al. Predicting novel histopathological microlesions in human epileptic brain through transcriptional clustering. *Brain* 2015; 138: 356–370.
279. Sillanpaa N, Saarinen JT, Rusanen H, et al. CT Perfusion ASPECTS in the Evaluation of Acute Ischemic Stroke: Thrombolytic Therapy Perspective. *Cerebrovasc Dis Extra* 2011; 1: 6–16.
280. De Reuck J, De Groote L, Van Maele G. Delayed transient worsening of neurological deficits after ischaemic stroke. *Cerebrovasc Dis* 2006; 22: 27–32.
281. Fan Y, Deng P, Wang Y-C, et al. Transient cerebral ischemia increases CA1 pyramidal neuron excitability. *Exp Neurol* 2008; 212: 415–21.
282. Pinard E, Nallet H, MacKenzie ET, et al. Penumbral microcirculatory changes associated with peri-infarct depolarizations in the rat. *Stroke* 2002; 33: 606–612.
283. Hamidou B, Aboa-Eboulé C, Durier J, et al. Prognostic value of early epileptic seizures on mortality and functional disability in acute stroke: The Dijon Stroke Registry (1985-2010). *J Neurol* 2013; 260: 1043–1051.
284. Sheorajpanday RVA, Nagels G, Weeren AJTM, et al. Reproducibility and clinical relevance of quantitative EEG parameters in cerebral ischemia: A basic approach. *Clin Neurophysiol* 2009; 120: 845–855.
285. Cuspineda E, Machado C, Galán L, et al. QEEG prognostic value in acute stroke. *Clin EEG Neurosci* 2007; 38: 155–160.
286. Westhall E, Rossetti AO, Stammet P, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. 2016; 0: 1–10.
287. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. *Circ Res*; 120.
288. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. *Cerebrovasc Dis* 2003; 16 Suppl 1: 14–9.
289. Frankel M, Morgenstern L, Kwiatkowski T, et al. Predicting prognosis after stroke: A placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA stroke trial. *Neurology* 2000; 55: 952–959.
290. Hankey GJ, Spiesser J, Hakimi Z, et al. Rate, degree, and predictors of recovery from disability following ischemic stroke. *Neurology* 2007; 68: 1583–1587.
291. Konig IR, Ziegler A, Bluhmki E, et al. Predicting long-term outcome after acute

ischemic stroke: A simple index works in patients from controlled clinical trials. *Stroke* 2008; 39: 1821–1826.
292. Finnigan S, van Putten MJAM. EEG in ischaemic stroke: Quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. *Clin Neurophysiol* 2013; 124: 10–19.
293. Sainio K, Stenberg D, Keskimaki I, et al. Visual and spectral EEG analysis in the evaluation of the outcome in patients with ischemic brain infarction. *Electroencephalogr Clin Neurophysiol* 1983; 56: 117–124.
294. Cillessen JP, van Huffelen a C, Kappelle LJ, et al. Electroencephalography improves the prediction of functional outcome in the acute stage of cerebral ischemia. *Stroke* 1994; 25: 1968–72.
295. Cuspineda E, Machado C, Aubert E, et al. Predicting outcome in acute stroke: a comparison between QEEG and the Canadian Neurological Scale. *Clin Electroencephalogr* 2003; 34: 1–4 ST–Predicting outcome in acute stroke: a co.
296. Finnigan SP, Walsh M, Rose SE, et al. Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. *Clin Neurophysiol* 2007; 118: 2525–2532.
297. Diedler J, Sykora M, Jüttler E, et al. EEG power spectrum to predict prognosis after hemicraniectomy for space-occupying middle cerebral artery infarction. *Cerebrovasc Dis* 2010; 29: 162–169.
298. Sheorajpanday RVA, Nagels G, Weeren AJTM, et al. Additional value of quantitative EEG in acute anterior circulation syndrome of presumed ischemic origin. *Clin Neurophysiol* 2010; 121: 1719–1725.
299. Sheorajpanday RVA, Nagels G, Weeren AJTM, et al. Quantitative EEG in ischemic stroke: Correlation with functional status after 6months. *Clin Neurophysiol* 2011; 122: 874–883.
300. Finnigan SP, Rose SE, Walsh M, et al. Correlation of quantitative EEG in acute ischemic stroke with 30-day NIHSS score: comparison with diffusion and perfusion MRI. *Stroke* 2004; 35: 899–903.
301. Bentes C, Martins H, Peralta AR, et al. Epileptic manifestations in stroke patients treated with intravenous alteplase. *Eur J Neurol* 2017; 24: 755–761.
302. Bentes C, Martins H, Peralta AR, et al. Post-stroke seizures are clinically underestimated. *J Neurol* 2017; 264: 1978–1985.
303. Noachtar S, Binnie C, Ebersole J, et al. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999; 52: 21–41.
304. Bentes C, Peralta AR, Martins H, et al. Seizures, electroencephalographic abnormalities, and outcome of ischemic stroke patients. *Epilepsia Open* 2017; 1–12.
305. Szelies B, Mielke R, Kessler J, et al. Prognostic relevance of quantitative topographical EEG in patients with poststroke aphasia. *Brain Lang* 2002; 82: 87–94.
306. Schleiger E, Sheikh N, Rowland T, et al. Frontal EEG delta/alpha ratio and screening for post-stroke cognitive deficits: The power of four electrodes. *Int J Psychophysiol* 2014; 94: 19–24.
307. Foreman B, Claassen J. Quantitative EEG for the detection of brain ischemia. Critical care 2012:16 (2):216.
308. Kaplan PW, Rossetti AO. EEG patterns and imaging correlations in encephalopathy: encephalopathy part II. *J Clin Neurophysiol* 2011; 28: 233–51.
309. Diedler J, Sykora M, Bast T, et al. Quantitative EEG correlates of low cerebral perfusion in severe Stroke. *Neurocrit Care* 2009; 11: 210–216.

310. Rathakrishnan R, Gotman J, Dubeau F, et al. Using continuous electroencephalography in the management of delayed cerebral ischemia following subarachnoid hemorrhage. *Neurocrit Care* 2011; 14: 152–161.
311. Finnigan SP, Rose SE, Chalk JB. Rapid EEG changes indicate reperfusion after tissue plasminogen activator injection in acute ischaemic stroke. *Clin Neurophysiol* 2006; 117: 2338–2339.
312. Tecchio F, Pasqualetti P, Zappasodi F, et al. Outcome prediction in acute monohemispheric stroke via magnetoencephalography. *J Neurol* 2007; 254: 296–305.
313. Assenza G, Zappasodi F, Pasqualetti P, et al. A contralesional EEG power increase mediated by interhemispheric disconnection provides negative prognosis in acute stroke. *Restor Neurol Neurosci* 2013; 31: 177–188.
314. Finnigan S, Wong A, Read S. Defining abnormal slow EEG activity in acute ischaemic stroke: delta/alpha ratio as an optimal QEEG index. *Clin Neurophysiol* 2015; 127: 1452–1459.
315. Sheorajpanday RVA, Nagels G, Weeren AJTM, et al. Quantitative EEG in ischemic stroke: Correlation with infarct volume and functional status in posterior circulation and lacunar syndromes. *Clin Neurophysiol* 2011; 122: 884–890.
316. Schneider AL, Jordan KG. Regional attenuation without delta (RAWOD): a distinctive EEG pattern that can aid in the diagnosis and management of severe acute ischemic stroke. *Am J Electroneurodiagnostic Technol* 2005; 45: 102–17.
317. de Vos CC, Maarseveen SM Van, Brouwers PJ a M, et al. Continuous EEG Monitoring During Thrombolysis in Acute. *J Clin Neurophysiol* 2008; 25: 77–82.
318. Bentes C, Canhão P, Peralta AR, et al. Usefulness of EEG for the differential diagnosis of possible transient ischemic attack. *Clin Neurophysiol Pract* 2018; 3: 11–19.
319. Bentes C, Rodrigues FB, Sousa D, et al. Frequency of post-stroke electroencephalographic epileptiform activity – a systematic review and meta-analysis of observational studies. *Eur Stroke J* 2017; 2: 361–368.
320. Beghi E, D'Alessandro R, Beretta S, et al. Incidence and predictors of acute symptomatic seizures after stroke. *Neurology* 2011; 77: 1785–1793.
321. Walker MC, Kovac S. Seize the moment that is thine: how should we define seizures? *Brain* 2015; 138: 1127–1128.
322. Bentes C, Franco AC, Peralta AR, et al. Epilepsia partialis continua after an anterior circulation ischaemic stroke. *Eur J Neurol* 2017; 24: 929–934.
323. Pitkanen A, Engel J. Past and Present Definitions of Epileptogenesis and Its Biomarkers. *Neurotherapeutics* 2014; 11: 231–241.
324. Pitkänen A, Löscher W, Vezzani A, et al. Advances in the development of biomarkers for epilepsy. *Lancet Neurol* 2016; 15: 843–856.
325. Bentes C, Martins H, Peralta AR, et al. Early EEG predicts poststroke epilepsy. *Epilepsia Open* 2018; 3: 0–3.
326. Pitkänen A, Nehlig A, Brooks-Kayal AR, et al. Issues related to development of antiepileptogenic therapies. *Epilepsia* 2013; 54: 35–43.
327. Lamy C, Domigo V, Semah F, et al. Early and late seizures after cryptogenic ischemic stroke in young adults. *Neurology* 2003; 60: 400–4.
328. Gasparini S, Ferlazzo E, Beghi E, et al. Epilepsy associated with Leukoaraiosis mainly affects temporal lobe: a casual or causal relationship? *Epilepsy Res* 2015; 109: 1–8.
329. Chang C-S, Liao C-H, Lin C-C, et al. Patients with epilepsy are at an increased risk of subsequent stroke: a population-based cohort study. *Seizure* 2014; 23: 377–81.

330. Beniczky S, Aurlien H, Brøgger JC, et al. Standardized computer-based organized reporting of EEG: SCORE – Second version. *Clin Neurophysiol* 2017; 128: 2334–2346.
331. Kane N, Acharya J, Benickzy S, et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. *Clin Neurophysiol Pract* 2017; 2: 170–185.
332. Herman ST, Abend NS, Bleck TP, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I: Indications. *J Clin Neurophysiol* 2015; 32: 87–95.
333. Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part II: personnel, technical specifications, and clinical practice. *J Clin Neurophysiol* 2015; 32: 96–108.
334. Alvarez V, Sierra-Marcos A, Oddo M, et al. Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. *Crit Care* 2013; 17: R190.
335. Hartings J, Williams A, Tortella F. Occurrence of nonconvulsive seizures, periodic epileptiform discharges, and intermittent rhythmic delta activity in rat focal ischemia. *Exp Neurol* 2003; 179: 139–149.
336. Friedman DE, Schevon C, Emerson RG, et al. Cyclic electrographic seizures in critically ill patients. *Epilepsia* 2008; 49: 281–287.
337. Klonowski W. Everything you wanted to ask about EEG but were afraid to get the right answer. *Nonlinear Biomed Phys* 2009; 3: 1–5.
338. Thevathasan A, Naylor J, Churilov L, et al. Association between hemorrhagic transformation after endovascular therapy and poststroke seizures. *Epilepsia* 2018; 59: 403–409.
339. Hauser RM, Henshall DC, Lubin FD. The Epigenetics of Epilepsy and Its Progression. *Neuroscientist* 2018; 24: 186–200.
340. Kobow K, Blumcke I. Epigenetics in epilepsy. *Neurosci Lett* 2018; 667: 40–46.
341. Kassis H, Shehadah A, Chopp M, et al. Epigenetics in stroke recovery. *Genes (Basel)* 2017; 8: 1–1

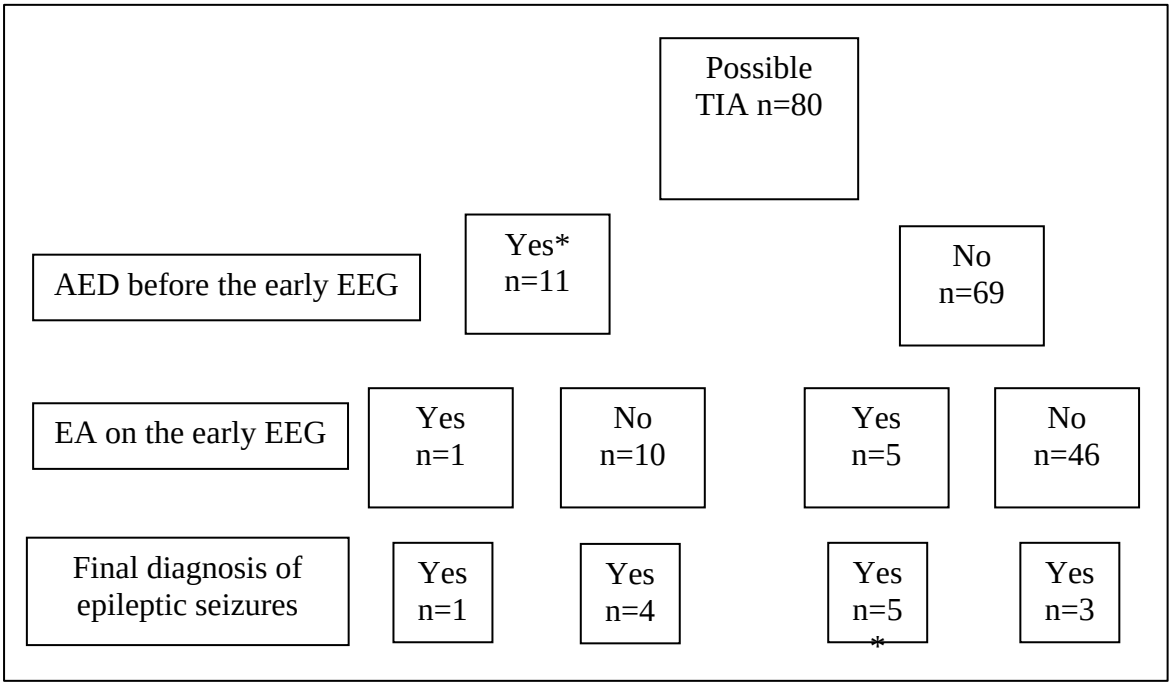
XVI. APPENDICES

"There is no real ending. It's just the place where you stop the story"

Frank Herbert

From Project 1 (Usefulness of EEG for the differential diagnosis of possible transient ischaemic attack)**:**

Appendix A. Antiepileptic drugs, epileptiform activity in the early EEG and the final diagnosis of epileptic seizures



Legend to appendix A: EA - Epileptiform Activity / TIA - Transient Ischaemic Attacks / AED - antiepileptic drug (including benzodiazepine) / EA - epileptiform activity / * Three patients were under AED for neuropathic pain, two medicated with phenytoin due to well-controlled and semiologically different seizures from the possible TIA under study and six with benzodiazepines for anxiety or insomnia.

From Project 2 (Frequency of post-stroke EEG epileptiform activity - a systematic review and meta-analysis of observational studies)**:**

Appendix B. Search Strategies:

Embase

1. exp cerebrovascular disease/ or ((Cerebrovascular$ adj1 Disorder$) or stroke$ or ((intracran$ or cereb$ or brain or Subarachno$) adj1 (Infarct$ or Ischemi$ or Ichaemi$ or Hematom$ or Haematom$ or Hemorrhag$ or Haemorrhag$ or thrombos$ or emboli$))).ti,ab.
2. exp focal epilepsy/ or exp generalized epilepsy/ or exp traumatic epilepsy/ or exp reflex epilepsy/ or exp seizure/ or exp epileptic state/ or (((partia$ or focal) adj2 epilep$) or (genera$ adj4 epilep$) or (traumatic adj2 epilep$) or (reflex$ adj2 epilep$) or seizur$ or (statu$ adj2 epilep$)).ti,ab.
3. exp cohort analysis/ or exp longitudinal study/ or exp prospective study/ or exp follow up/ or exp case control study/ or (cohort$ or (case$ adj10 control$)).tw.
4. 1 and 2 and 3
5. (animal$ not human$).sh,hw.
6. 4 not 5
7. limit 6 to exclude medline journals

MEDLINE

1. exp Cerebrovascular Disorders/ or ((Cerebrovascular$ adj1 Disorder$) or stroke$ or ((intracran$ or cereb$ or brain or Subarachno$) adj1 (Infarct$ or Ischemi$ or Ichaemi$ or Hematom$ or Haematom$ or Hemorrhag$ or Haemorrhag$ or thrombos$ or emboli$))).ti,ab.
2. exp Epilepsies, Partial/ or exp Epilepsy, Generalized/ or exp Epilepsy, Post-Traumatic/ or exp Epilepsy, Reflex/ or exp Seizures/ or exp Status Epilepticus/ or ((partia$ adj2 epilep$) or (genera$ adj4 epilep$) or (post-traumatic adj2 epilep$) or (reflex$ adj2 epilep$) or seizur$ or (statu$ adj2 epilep$)).ti,ab.
3. exp cohort studies/ or exp case-control studies/ or (cohort$ or (case$ adj10 control$)).tw.
4. epidemiologic methods/
5. limit 4 to yr=1966-1989

6. 3 or 5
7. 1 and 2 and 6
8. Animals/ not Human/
9. 7 not 8

PsycINFO

1. exp Cerebrovascular Disorders/ or ((Cerebrovascular$ adj1 Disorder$) or stroke$ or ((intracran$ or cereb$ or brain or Subarachno$) adj1 (Infarct$ or Ischemi$ or Ichaemi$ or Hematom$ or Haematom$ or Hemorrhag$ or Haemorrhag$ or thrombos$ or emboli$))).ti,ab.
2. exp Epilepsy/ or exp Seizures/ or ((partia$ adj2 epilep$) or (genera$ adj4 epilep$) or (post-traumatic adj2 epilep$) or (reflex$ adj2 epilep$) or seizur$ or (statu$ adj2 epilep$)).ti,ab.
3. exp Cohort Analysis/ or (cohort$ or (case$ adj10 control$)).tw.
4. 1 and 2 and 6
5. Animals/ not Human/
6. 7 not 8

Web of Science

TOPIC: (Cerebrovascular Disorder* OR Cerebrovascular Disease* OR stroke* OR ((intracran* OR cereb* OR brain OR Subarachno*) NEAR/1 (Infarct* OR Ischemi* OR Ichaemi* OR Hematom* OR Haematom* OR Hemorrhag* OR Haemorrhag* OR thrombos* OR emboli*))) *AND* TOPIC: (((Generali OR Partial OR Focal OR Trauma* OR Reflex OR Stat*) NEAR/2 Epilep*) OR Seizure*) *AND* TOPIC: (Cohort* OR Case-Control* OR (case* NEAR/10 control*))

Timespan: All years. Indexes: SCI-EXPANDED, CPCI-S.

Open Grey

(Cerebrovascular Disorder* OR Cerebrovascular Disease* OR stroke* OR ((intracran* OR cereb* OR brain OR Subarachno*) NEAR/1 (Infarct* OR Ischemi* OR Ichaemi* OR Hematom* OR Haematom* OR Hemorrhag* OR Haemorrhag* OR thrombos* OR emboli*))) AND (((Generali OR Partial OR Focal OR Trauma* OR Reflex OR Stat*) NEAR/2 Epilep*) OR Seizure*) AND (Cohort* OR Case-Control* OR (case* NEAR/10 control*)

From Project 2 (Frequency of post-stroke EEG epileptiform activity - a systematic review and meta-analysis of observational studies)**:**

Appendix C. Included studies

1. Arboix A, Garcia-Eroles L, Massons JB, Oliveres M, Comes E. Predictive factors of early seizures after acute cerebrovascular disease. *Stroke; a journal of cerebral circulation*. 1997;28:1590-1594
2. Carrera E, Michel P, Despland PA, Maeder-Ingvar M, Ruffieux C, Debatisse D, et al. Continuous assessment of electrical epileptic activity in acute stroke. *Neurology*. 2006;67:99-104
3. Chen Y, Chen L, Tao Y, Han M, Cui C, Liu S. Post-stroke seizures in consecutive elderly stroke patients. *Neural Regeneration Research*. 2011;6:717-720
4. Claassen J, Hirsch LJ, Frontera JA, Fernandez A, Schmidt M, Kapinos G, et al. Prognostic significance of continuous eeg monitoring in patients with poor-grade subarachnoid haemorrhage. *Neurocritical Care*. 2006;4:103-112
5. Claassen J, Jette N, Chum F, Green R, Schmidt M, Choi H, et al. Electrographic seizures and periodic discharges after intracerebral haemorrhage. *Neurology*. 2007;69:1356-1365
6. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology*. 2004;62:1743-1748
7. Dhanuka AK, Misra UK, Kalita J. Seizures after stroke: A prospective clinical study. *Neurology India*. 2001;49:33-36
8. Garrett MC, Komotar RJ, Starke RM, Merkow MB, Otten ML, Connolly ES. Predictors of seizure onset after intracerebral haemorrhage and the role of long-term antiepileptic therapy. *Journal of Critical Care*. 2009;24:335-339
9. Lindgren C, Nordh E, Naredi S, Olivecrona M. Frequency of non-convulsive seizures and non-convulsive status epilepticus in subarachnoid haemorrhage patients in need of controlled ventilation and sedation. *Neurocritical Care*. 2012;17:367-373
10. Little AS, Kerrigan JF, McDougall CG, Zabramski JM, Albuquerque FC, Nakaji P, et al. Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid haemorrhage. *Journal of Neurosurgery*. 2007;106:805-811

11. Naidech AM, Garg RK, Liebling S, Levasseur K, Macken MP, Schuele SU, et al. Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke; a journal of cerebral circulation*. 2009;40:3810-3815
12. O'Connor KL, Westover MB, Phillips MT, Iftimia NA, Buckley DA, Ogilvy CS, et al. High risk for seizures following subarachnoid hemorrhage regardless of referral bias. *Neurocritical Care*. 2014;21:476-482
13. Srinivasan S, Shin H, Chou SH, Pennell PB, Dworetzky BA, Lee JW. Seizures and antiepileptic drugs in patients with spontaneous intracerebral hemorrhages. *Seizure*. 2013;22:512-516
14. Strzelczyk A, Haag A, Raupach H, Herrendorf G, Hamer HM, Rosenow F. Prospective evaluation of a post-stroke epilepsy risk scale. *Journal of Neurology*. 2010;257:1322-1326
15. Swisher CB, White CR, Mace BE, Dombrowski KE, Husain AM, Kolls BJ, et al. Diagnostic accuracy of electrographic seizure detection by neurophysiologists and non-neurophysiologists in the adult icu using a panel of quantitative eeg trends. *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*. 2015;32:324-330
16. Velioglu SK, Ozmenoglu M, Boz C, Alioglu Z. Status epilepticus after stroke. *Stroke; a journal of cerebral circulation*. 2001;32:1169-1172
17. Vespa PM, O'Phelan K, Shah M, Mirabelli J, Starkman S, Kidwell C, et al. Acute seizures after intracerebral hemorrhage: A factor in progressive midline shift and outcome. *Neurology*. 2003;60:1441-1446

From Project 3 (Post-stroke seizures are clinically underestimated)**:**

Appendix D. Video-EEG technical protocol

The EEG record followed the recommendations of the IFCN [207], ILAE [208], ACNS [209,210] and LPCE [3]. Video-EEG was performed by a Nihon-Kohden device (Neurofax EEG-1200) with a sampling frequency of 1000 Hz. We used the international 10/10 electrode placement system and recorded at least 64 EEG channels. An electrode cap adapted to the patient's head size was used and the correct position of the electrodes was confirmed. Two electrooculogram channels and one chin electromyogram channel were also recorded using silver chloride electrodes. If involuntary movements were observed, additional EMG electrodes were placed allowing EMG/EEG synchronized recording. The electrode impedance was less than 5 KOhms at the beginning of the record and was revaluated whenever a compatible artifact was detected. The total recording period was at least 35 minutes of wakefulness, including activation tests. Sleep was recorded whenever possible at the end of the exam. The maximum duration of the test was 60 minutes. The acquisition parameters were: sensitivity at 10 µV/mm; time constant at 0.3s; high frequency filter at 70 Hz. 50Hz filter was used when other attempts to eliminate electric artifact failed. The record included 3 different montages (bipolar longitudinal, bipolar transverse and referential). All attempts to fix EEG artifacts by the technical team were annotated in the record itself. Except in the final phase of the record, the technician tried to keep the patient awake or at his/her maximum alert level. Changes in consciousness level were also recorded. For patients in stupor/coma, the auditory and somatosensory stimulation was used systematically (and recorded). In the event of repetitive epileptiform or periodic discharges, delta rhythmic activity and spatiotemporal evolution of rhythmic or periodic activity, even in the absence of obvious behavioural manifestations, the EEG technician called medical staff who looked for subtle clinical epileptiform manifestations and systematically assessed consciousness level, orientation, response to simple motor orders (open and close your eyes, open and close both hands), naming of objects (pen, clock), numbers count in descending order, verbal memory and muscle strength of the upper limbs during the event.

All records were performed by EEG technicians with experience in video-EEG and EEG records in acute brain lesion patients, under medical supervision, using the following technical protocol:

I. In the longitudinal bipolar montage:

1st Lying patient with eyes closed: 5 minutes

2nd Opening eyelids for 5 seconds and ocular fixation on one point, then closing eyelids 25 seconds (opening/closing of the eyelids was done manually by the technician for an uncooperative patient). Twice repeated.

3rd Patient lying with eyes closed: 5 minutes

4th Hyperventilation for 3 minutes (the patient's effort was graduated: weak, medium, good, excellent). It was not made in the presence of contraindications.

II. In bipolar transverse montage:

5th Patient lying with eyes closed: 5 minutes

6th Opening eyelids for 5 seconds and ocular fixation on one point, then closing eyelids 25 seconds (opening/closing of the eyelids was done manually by the technician for an uncooperative patient). Twice repeated.

III. In "average" montage:

7th Patient lying with eyes closed: 5 minutes

8th Intermittent photic stimulation performed with eyes open and closed with a photic stimulator at 30 cm in front of the eyes and using stimulation frequencies between 1 and 30 Hz, with 10 seconds range between stimuli.

9th Patient lying with eyes closed: 5 minutes

10th Patient lying with eyes closed until the end of the exam. Sleep was allowed in this period. Can be registered in the transverse bipolar montage.

Whenever myoclonus was observed during the neurological examination, synchronized EMG record of the involuntary movement was added to the exam. The EEG record in that situation included not only eye-lid opening and closure, hyperventilation, photic stimulation, but also manoeuvres to elicit myoclonus, as previously observed in the neurological evaluation to allow "jerk-lock back-average" analysis.

From Project 3 (Post-stroke seizures are clinically underestimated)

Appendix E. Clinical and imaging characteristics of patients with electrographic seizures during hospital admission

	Pt1	Pt2	Pt3	Pt4	Pt5	Pt6	Pt7
Age (years)	74	69	78	49	66	77	78
Admission NIHSS[a]	17	15	23	12	18	7	8
Intravenous alteplase treatment	no	yes	yes	yes	yes	yes	yes
Exclusively cortical lesion	no	no	no	no	no	no	no
Exclusively subcortical lesion	no	no	no	no	no	no	no
Cortical and subcortical lesion	yes	yes	yes	yes	yes	yes	yes
1st CT[b] ASPECTS[c] - Total - Cortical territories of this scale	 4 1	 6 6	 9 6	 5 2	 7 4	 9 3	 9 6
Day after stroke with seizures	2.nd 6.st	3rd	2.nd	2.nd	2.nd	6.th 7.th 8.th	2.nd
Acute symptomatic seizures (clinically)	no	no	no	no	no	yes	yes
NCSE[d] criteria	no	yes	no	yes	no	yes	no
AED[e] at discharge	no	NA[g]	no	yes	no	yes	no
mRS[f] at discharge	4	6	5	4	4	4	1
Unprovoked seizures	no	NA	no	yes	yes	yes[h]	no
mRS at 12 months	6	6	6	4	3	3	0

Legend to appendix E: [a]NIHSS - National Institutes of Health Stroke Scale score ; [b]1stCT - 1st CT scan obtain at the emergency department; [c]ASPECTS - Alberta Stroke Program Early CT Score; [d]NCSE - Non-convulsive *status epilepticus*; [e]AED - Antiepileptic drug ; [f]mRS - modified Rankin Scale score ; [g]NA – Non applicable; [h]At 12 months after stroke this patient had focal motor seizures of the left limbs and myoclonus of the upper left limb (contralateral to the ischaemic lesion) with cortical correlate by back-average analysis technique, according to the diagnosis of EPC [1]

Appendix E reference: 1. Bentes C, Franco AC, Peralta AR, et al (2017) Epilepsia partialis continua after an anterior circulation ischaemic stroke. 1–6. doi: 10.1111/ene.13310

From Project 3 (Post-stroke seizures are clinically underestimated)**:**

Appendix F. Continuous EEG (cEEG) studies in stroke patients

	Vespa et al. 2003 Los Angeles, USA[1]	Claassen et al. 2004 New York, USA [2]	Pandian et al. 2004 Rochester, USA [3]	Carrera et al. 2006 Lausanne, Switzerland [4]	Kurtz et al. 2014 New York, USA [5]	Swisher et al. 2015 Durham, USA [6]	Westover et al. 2015 Boston, USA [7]
Study design	Prospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Setting	ICU[d]	ICU + non-ICU[e]	ICU	Stroke Unit	Surgical ICU	ICU + non-ICU	NK[f]
Type of Stroke / other CNS[a] lesion	46 ischaemic + 63 parenchymal haemorrhages	56 ischaemic + 45 parenchymal haemorrhages + other lesions	12 ischaemic + 7 parenchymal haemorrhages + other lesions	91 ischaemic + 9 parenchymal haemorrhages	23 ischaemic + 6 parenchymal haemorrhages + other lesions	17 ischaemic + 19 parenchymal haemorrhages + other lesions	59 ischaemic + 44 parenchymal haemorrhages + other lesions
Sample Size	109	570	105	100	154	234	625
ASS[b]	19,3% (89%<72h)	19% (56%<1h; 88% < 24h; 93% < 48h)	16%	2%	16%	21% (45%<1/2h; 80% < 24h; 92% < 48h; 98% < 98h)	27% (58%<1/2h)
	ischaemic stroke: 6%	ischaemic stroke: 11 %	ischaemic stroke: NK	ischaemic stroke: NK	ischaemic stroke: 22%	ischaemic stroke: 17.6%	ischaemic stroke: 27%
	parenchymal haemorrhages: 27.8%	parenchymal haemorrhages: 13%	parenchymal haemorrhages: NK	parenchymal haemorrhages: NK	parenchymal haemorrhages: 17%	parenchymal haemorrhages: 21.0%	parenchymal haemorrhages: 59%
US[c]	NK	NK	NK	NK	NK	NK	NK

	Vespa et al. 2003 Los Angeles, USA[1]	Claassen et al. 2004 New York, USA [2]	Pandian et al. 2004 Rochester, USA [3]	Carrera et al. 2006 Lausanne, Switzerland [4]	Kurtz et al. 2014 New York, USA [5]	Swisher et al. 2015 Durham, USA [6]	Westover et al. 2015 Boston, USA [7]
Follow-up time	NK	NK	Mean: 7 months (1-54)	NK	NK	NK	NK
Status Epilepticus	NK	10% ischaemic stroke: 7 % parenchymal haemorrhages: 9%	67.6%	NK	5%	26%	
EEG Settings	cEEG	cEEG	cEEG preceded by 30 min. EEG	cEEG	cEEG	cEEG	cEEG
	14 channels	21 channels	21 channels	21 channels	10 channels	21 channels	21 channels
	Duration: NK[f]	Duration: NK	Duration: N K	Mean duration: 17h34m (1h12m-37h10m)	Duration: >12h	Duration: 24 - 48h	Duration: >18 h
	When after stroke: <24h	When after stroke: NK	When after stroke: NK	When after stroke: NK	When after stroke: >24 h (69% >48h)	When after stroke: NK	When after stroke: NK
EEG Results	"76% patients experienced only Electrographic seizures"	Seizures on cEEG: 19,3% "PLED[g], GPED[h], and burst suppression were frequently seen in patients with seizures on cEEG monitoring" "21% of patients with PLED had their first seizure after the first 24 h of cEEG compared with 8% in those without PLED"	EEG/cEEG: IEA[i] - 49.5%/ 55,2% PLED - 19%/21.9% Seizures - 11.4%/26.7% "Electrographic seizures were more commonly observed with the Video-EEG than with routine EEG"	IEA: 14% PLED: 3% IEA or PLED:17% Electrographic seizures: 2% "3 factors increase the hazard of electrical epileptic activity: NIHSS score on admission; cortical involvement and thrombolysis"	PLED: 31.6% Seizures on cEEG: 16 %	"if generalized slowing on the EEG unlikelihood to develop seizures on subsequent cEEG" "PD[j], GPD[k], burst suppression, focal IEA on the initial 30 minutes of cEEG had a high association with seizures later in the monitoring"	IEA < 30 min.: 25% of patients with seizures and 8% of patients without seizures "epileptiform abnormalities very early in the cEEG accurately stratified the risk of seizures within 72 h" "The 72 h risk for seizures decays to <5% over 2 h in patients without epileptiform EEG abnormalities"

Legend to appendix F: [a]CNS - central nervous system; [b]ASS - Acute Symptomatic Seizures. ASS definition was not always similar in different studies. The frequency of ASS includes the frequency of clinical and/or Electrographic seizures; [c]US - Unprovoked seizures. US definition was not always similar in different studies; [d]ICU - Intensive care unit; [e]Non-ICU - Hospitalar department with a non-intensive care profile; [f]NK - not known; [g]PLED - periodic lateralized epileptiform discharges; [h]GPED - generalized epileptiform discharges; [i]IEA - interictal epileptiform activity; [j]PD - lateralized periodic discharges; [j]GPD - generalized periodic discharges

Appendix F references:

1. Vespa PM, O'Phelan K, Shah M, et al (2003) Acute seizures after intracerebral haemorrhage: a factor in progressive midline shift and outcome. Neurology 60:1441–1446. doi: 10.1212/01.WNL.0000063316.47591.B4

2. Claassen J, Mayer SA, Kowalski RG, et al (2004) Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 62:1743–1748. doi: 10.1212/01.WNL.0000125184.88797.62

3. Pandian JD, Cascino GD, So EL, et al (2004) Digital Video-Electroencephalographic Monitoring in the Neurological-Neurosurgical Intensive Care Unit. ARCH NEUROL 61:1090–1094.

4. Carrera E, Michel P, Despland P, et al (2006) Continuous assessment of electrical epileptic activity in acute stroke. Neurology 67:99–104. doi: 10.1212/01.wnl.0000223361.90278.ca

5. Kurtz P, Gaspard N, Wahl AS, et al (2014) Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med 40:228–234. doi: 10.1007/s00134-013-3149-8

6. Swisher CB, Shah D, Sinha SR, Husain AM (2015) Baseline EEG pattern on continuous ICU EEG monitoring and incidence of seizures. J Clin Neurophysiol 32:147–51. doi: 10.1097/WNP.0000000000000157

7. Westover MB, Shafi MM, Bianchi MT, et al (2015) The probability of seizures during EEG monitoring in critically ill adults. Clin Neurophysiol 126:463–471. doi: 10.1016/j.clinph.2014.05.037

From Project 3 (Post-stroke seizures are clinically underestimated)**:**

Appendix G. Short duration (spot) EEG in stroke patients

	Holmes 1980 Newington, USA [1]	Ryglewicz et al. 1990 Warsaw, Poland [2]	Dhanuka et al. 2001 Ludhiana, India [3]	Velioglu et al. 2001 Trabzon, Turkey [4]	De Reuck et al. 2006 Ghent, Belgium [5]	Strzelczyk et al. 2010 Marburg Germany [6]	Mecarelli et al. 2011 Roma, Italy [7]	Bentes et al. 2017 Lisbon, Portugal
Study design	Retrospective	Retrospective case-control	Prospective case series	Retrospective cohort	Retrospective case-control	Prospective cohort	Prospective cohort	Prospective cohort
Setting	NK[d]	NK	Neurology Department	NK	Neurology Department? Stroke Unit? and ICU[e]	Neurology Department	Neurology Department, Stroke Unit and ICU	Stroke Unit
Type of Stroke / other CNS[a] lesion	ischaemic	ischaemic	20 ischaemic + 15 parenchymal haemorrhages	NK ischaemic + NK parenchymal haemorrhages	ischaemic (non-lacunar)	NK ischaemic + NK parenchymal haemorrhages	177 ischaemic + 55 parenchymal haemorrhages	151 ischaemic (anterior circulation)
Sample Size	500 patients 250 with EEG	50 stroke patients with seizures compared to 50 patients without seizures	35 patients with seizures (13%)	1174 patients (consecutive)	110 stroke patients with seizures (69 with EEG) compared to 275 patients without seizures	264 patients (consecutive) 148 with EEG	232 patients (non-consecutive)	151 patients (consecutive) 151 with EEG
ASS[a]	8%	NK	77% (63% < 24h)	121 ischaemic and 59 haemorrhagic stroke patients with seizures	12 patients	4.5% (58% < 24h)	6.5% (100%<24h)	14.6% (52.1% < 24h)
US[b]	12.8%	NK	23%		98 patients	6.4%	NK	15.2%

	Holmes 1980 Newington, USA [1]	Ryglewicz et al. 1990 Warsaw, Poland [2]	Dhanuka et al. 2001 Ludhiana, India [3]	Velioglu et al. 2001 Trabzon, Turkey [4]	De Reuck et al. 2006 Ghent, Belgium [5]	Strzelczyk et al. 2010 Marburg Germany [6]	Mecarelli et al. 2011 Roma, Italy [7]	Bentes et al. 2017 Lisbon, Portugal
Follow-up time	≥2 years	1 a 2 years	±6 years	3.7 years	22 months (4–98)	12 months	1 week	12 months
Status Epilepticus	NK	NK	NK	1.4% (0.6% acute; 0.85% remote)	14 patients (4/12 acute; 10/98 remote)	NK	10 patients	2.6%: acute 7%: remote
EEG Settings	Spot EEG	Spot EEG	Spot EEG	Spot EEG	Spot EEG	Spot EEG	Spot EEG	Spot EEG
	Number channels: NK	Channels number: NK	Channels number: NK	Channels number: NK	Channels number: 14	Channels number:	Channels number:	Channels number: 64
	Duration: NK	Duration: NK	Duration: NK	Duration: NK	Duration: NK	Duration: ≥ 23 m	Duration: <30 m	Duration: <60m
	When after stroke: 1st weak	When after stroke: NK	When after stroke: NK	When after stroke: NK	When after stroke: NK	When after stroke: NK	When after stroke: ≤ 24 h	When after stroke: ≤ 72 h / daily ≤ day 7 / discharge / 12 months
Neurophysiological Evaluation Results	"IEA[f] and PLED[g] more frequently found in patients with seizures vs. without seizures (26.9% vs. 2.0%)" "No EEG difference was found between ASS and US patients"	"IEA more frequently found in patients with epilepsy vs. without epilepsy (56% vs. 28%)"	IEA: 17.1% BA[h] slowing: 25.7% FSWA[i] or BA asymmetry: 22.9% "No EEG difference was found between ASS and US patients"	"No EEG differences was noted between seizure patients with and without *status epilepticus* "	"PLED[j], FIRDA[h] and BA diffuse slowing more frequent in stroke patients with seizures (5.8%, 24.6% and 21.7% vs. 0%, 1.1% and 5.1%)" "FIRDA and BA diffuse with a high risk to develop late-seizures, while the chance is reduced in those with a normal EEG"	IEA:11.5%	IEA: 10% PLED: 6% "Early epileptic manifestations were independently associated with PLED"	IEA : 10.6% PD[i]:17.9% EA[j]: 17.9% Electrographic seizures:4.6 %

Legend to appendix G: [a]CNS - central nervous system; [b]ASS - Acute Symptomatic Seizures. ASS definition was not always similar in different studies. The frequency of ASS includes the frequency of clinical and/or electrographic seizures; [c]US - Unprovoked seizures. US definition was not always similar in different studies; [d]NK - not known; [e]ICU - Intensive care unit; [f] IEA - interictal epileptiform activity; [g]PLED - periodic lateralized epileptiform discharges; [h]BA - background activity; [i]FSWA – focal slow wave activity; [j]PLED - periodic lateralized epileptiform discharges; [h]FIRDA - frontal intermittent rhythmic delta activity; [i]PD - periodic discharges; [i]EA – interictal and/or ictal epileptiform activity

Appendix G references:

1. Holmes GL (1980) The Electroencephalogram as a Predictor of Seizures following Cerebral Infarction. Clin Electroencephalogr 11:83–86.
2. Ryglewicz D EEG and CT findings is poststroke epilepsy.
3. Dhanuka a K, Misra UK, Kalita J (2001) Seizures after stroke: a prospective clinical study. Neurol India 49:33–6.
4. Velioglu SK, Ozmenoglu M, Boz C, Alioglu Z (2001) Status epilepticus after stroke. Stroke 32:1169–1172.
5. De Reuck J, Goethals M, Claeys I, et al (2006) EEG findings after a cerebral territorial infarct in patients who develop early- and late-onset seizures. Eur Neurol 55:209–213. doi: 10.1159/000093871
6. Strzelczyk A, Haag A, Raupach H, et al (2010) Prospective evaluation of a post-stroke epilepsy risk scale. J Neurol 257:1322–1326. doi: 10.1007/s00415-010-5520-9
7. Mecarelli O, Pro S, Randi F, et al (2011) EEG patterns and epileptic seizures in acute phase stroke. Cerebrovasc Dis 31:191–198. doi: 10.1159/000321872

From Project 4 (*Epilepsia Partialis Continua* after an anterior circulation ischaemic stroke)**:**

Appendix H. ASPECTS vascular territory in patients with middle cerebral artery territory limited infarct

ASPECTS Vascular Territory		**Number (%) of patients**
Subcortical	Lentiform nucleus	73 (58.9%)
	Caudate	45 (36.3%)
	Internal Capsula	48 (38.7%)
Cortical	Insular ribbon	81 (65.3%)
	M1	39 (31.5%)
	M2	63 (50.8%)
	M3	36 (29.0%)
	M4	30 (24.2%)
	M5	71 (57.3%)
	M6	48 (38.7%)

Legend to appendix H: M1 - anterior middle cerebral artery (MCA) cortex; M2 - MCA cortex lateral to the insular ribbon; M3 – posterior MCA cortex; M4, M5, M6 - anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, rostral to basal ganglia.

From Project 4 (*Epilepsia Partialis Continua* after an anterior circulation ischaemic stroke)**:**

Appendix I. Video 1 (digital only):
Link to video 1 - https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.13310 (ene13310-sup-0002-VideoS1.mov)
Video 1 description - Irregular, small amplitude, non-synchronized, subtle, mainly jerky movements of several fingers of patient 1, accentuated by posture, are observed

From Project 4 (*Epilepsia Partialis Continua* after an anterior circulation ischaemic stroke)

Appendix J. Video 2 (digital only):
Link to video 2 - https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.13310 (ene13310-sup-0003-VideoS2.mov)
Video 2 description - Irregular, small amplitude, non-synchronized, subtle, jerky movements of several fingers of patient 2 are observed

From Project 5 (Cortical myoclonus during intravenous thrombolysis for ischaemic stroke)**:**

Appendix K. Video 3 (digital only):
Link to video 3 - http://dx.doi.org/10.1016/j.ebcr.2014.09.004
Video 3 description - After rtPA bolus, involuntary movements of the upper paretic limb were noticed. The movements involved either the distal or the proximal muscles, independently, and could be jerk-like, irregular, myoclonic-like, or slow and brief.

From Project 6 (Epileptic manifestations in stroke patients treated and not-treated with intravenous alteplase)**:**

Appendix L. Clinical, imaging and neurophysiological characteristics of patients with paroxysmal clinical events during rtPA perfusion

Patients with paroxysmal clinical phenomena during alteplase perfusion	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4[a]**	**Patient 5**
Clinical characteristics					
Age (Years)	83	62	62	72	60
NIHSS at admission	23	20	9	11	18
Paroxysmal phenomenon semiology	Involuntary movements of the PLL	Consciousness disturbance and PUL clonus	PUL Myoclonus	PUL Myoclonus	PUL Myoclonus
Interruption of perfusion	No	**Yes**	No	No	No
Medication with AED	**Yes**	No	No	No	No
NIHSS after rtPA	23	37	6	12	17
Another event suggestive of seizures during hospitalization	No	No	No	No	No
NCSE Criteria	No	No	No	No	No
mRS at discharge	6	6	0	2	4
Unprovoked seizures	No	No	No	No	**Yes**
mRS at 12 months	6	6	1	2	3

Patients with paroxysmal clinical phenomena during alteplase perfusion	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4[a]**	**Patient 5**
Imaging Characteristics in the 2nd CT					
ASPECTS - Total - Cortical territories	 0 0	 9 7	 8 7	 5 2	 4 4
Exclusively cortical infarct	No	No	No	**Yes**	No
Exclusively subcortical infarct.	No	**Yes**	**Yes**	No	No
Islands of preserved cortex within the infarct	**Yes**	No	No	**Yes**	No
Haemorrhage	**Yes**	No	No	**Yes**	No
Neurophysiological characteristics					
1st EEG BA diffuse slowing	**Yes**	**Yes**	No	No	**Yes**
1st BA asymmetry	No	No	No	No	No
1st Suppression	**Yes**	**Yes**	No	No	No
1st FSWA	**Yes**	**Yes**	**Yes**	No	**Yes**
1st RSWA	No	**Yes**	No	No	No
1st PD	No	**Yes**	No	No	No
1st IEA	No	No	No	No	No
IEA and/or seizures in any EEG during hospitalization	No	No	No	No	No

Legend to appendix L: AED - anti-epileptic Drugs; ASPECTS - Alberta stroke program early CT score; BA - background activity; 1st EEG - EEG performed in the first 72 hours after stroke; 2nd CT scan - brain CT scan performed 24 hours after stroke; FSWA - focal slow wave activity; IEA - interictal epileptiform activity; mRS - modified Rankin scale; NCSE - nonconvulsive *status epilepticus*; NIHSS - National Institutes of Health Stroke Scale; PD - periodic discharges; PLL - Paretic Lower Limb; PUL - Paretic Upper Limb; RSWA - rhythmic slow wave activity; Suppression: focal or diffuse EEG suppression; **[a]** This case is reported in the literature [33]

From Project 7 (Early EEG predicts post-stroke epilepsy)**:**

Appendix M. Clinical and imaging characteristics and 1st EEG abnormalities (bivariate analysis)

Clinical and imaging characteristics	Age	Admission NIHSS[a]	1st CT ASPECTS[b]	1st CT Cortical ASPECTS[c]	Islands of preserved cortex within the infarct	Haemorrhage
1st EEG characteristics	p value					
BA[d] slowing	**0.001**	**<0.0005**	0.250	0.279	0.557	**0.009**
BA asymmetry	0.083	**<0.0005**	**0.005**	**0.004**	**0.024**	**0.039**
Suppression	0.065	0.053	0.052	0.098	0.420	0.078
FSWA[e]	0.038	**0.001**	0.202	0.160	0.464	0.701
RSWA[f]	0.941	0.746	**0.032**	0.353	0.741	1.000
PD[g]	0.224	**0.001**	0.083	0.094	0.741	0.249
IEA[g]	0.489	**0.046**	**0.024**	**0.043**	**0.006**	0.095

Legend to appendix M: [a]NIHSS - National Institutes of Health Stroke Scale score; [h]ASPECTS - Alberta Stroke Program Early CT Score; [c]Cortical ASPECTS - value in ASPECTS considering only the 7 cortical territories of this scale; [d]BA – background activity; [e]FSWA - focal slow wave activity; [f]RSWA - rhythmic slow wave activity; [g]PD –periodic discharges; [h]IEA - interictal epileptiform activity; bold values - $p<0.05$

From Project 7 (Early EEG predicts post-stroke epilepsy)**:**

Appendix N. Clinical, imaging characteristics and 1st EEG abnormalities in patients with (vs. without) EEG seizures during hospital stay (bivariate analysis)

Patients with (n=7) vs. without EEG seizures	p
Mean Age (SD[a])	0.528
Median admission NIHSS[b] (IQR[c])	0.476
1st CT[d] median ASPECTS[e] (IQR)	0.028
1st CT median CORTICAL[f] ASPECTS (IQR)	0.027
Islands of preserved cortex within the infarct	0.030
BA[g] slowing	1.000
BA asymmetry	0.135
Suppression	0.447
FSWA[h]	1.000
RSWA[i]	0.346
PD[j]	0.609
IEA[k]	0.161

Legend to appendix N: [a]SD - standard deviation; [b]NIHSS - National Institutes of Health Stroke Scale score; [c]IQR - interquartile range; [d]1st CT - 1st CT scan obtain at the emergency department; [e]ASPECTS - Alberta Stroke Program Early CT Score ; [f]Cortical ASPECTS - value in ASPECTS considering only the 7 cortical territories of this scale; [g]BA - background activity; [h]FSWA - focal slow wave activity; [i]RSWA - rhythmic slow wave activity; [j]PD - periodic discharges, [k]IEA - interictal epileptiform activity

From Project 7 (Early EEG predicts post-stroke epilepsy)**:**

Appendix O. Clinical, imaging and neurophysiological predictors of acute symptomatic seizures

Acute symptomatic seizures	**Yes**	**No**	**Bivariate analysis**[o] p OR[a]; 95% CI[b]	**Multivariate analysis**[p] p OR; 95% CI
Demographic and clinical characteristics (n=151)				
Number of patients	22	129		
Mean Age (SD[c])	70.4 (10.6)	66.8 (12.1)	0.194	NA
Median admission NIHSS[d] (IQR[e])	16.5 (10)	12 (10)	**0.033**	0.776 1.03; 0.98-1.11
Stroke aetiology: Cardio embolism	12 (54.5%)	65 (50.4%)	0.606	NA
Atherosclerosis	4 (18.2%)	33 (25.6%)		
Small vessels	0 (0.0%)	4 (3.1%)		
Undetermined	6 (27.3%)	23 (17.8%)		
Other	0 (0.0%)	4 (3.1%)		
Imaging stroke characteristics I				
Isolated MCA[f] territory infarct patients (n=146)				
Number of patients	20	126		
1st CT[g] median ASPECTS[h] (IQR)	8.5 (3)	9 (2)	**0.004**	**0.019** **0.73; 0.56-0.95**
1st CT median CORTICAL[i] ASPECTS (IQR)	5.5 (3)	6 (2)	**0.004**	**0.019** **0.73; 0.56-0.95**

Acute symptomatic seizures	**Yes**	**No**	**Bivariate analysis**[o] p OR[a]; 95% CI[b]	**Multivariate analysis**[p] p OR; 95% CI
Imaging stroke characteristics II				
Anterior circulation ischaemic stroke patients with a 2nd CT scan (n=129)				
Number of patients	22	107		
Islands of preserved cortex within the infarct	8 (36.4%)	18 (16.8%)	0.037 2.82; 1.03-7.72	0.239 2.01; 0.63-6.46
Haemorrhage	5 (22.7%)	18 (16.8%)	0.544 1.45; 0.48-4.45	NA
1st EEG characteristics I (n=151)				
Number of patients	22	129		
BA[j] diffuse slowing	14 (63.6%)	43(33.3%)	**0.007** **3.50; 1.36-8.98**	0.094 2.58; 0.85-7.85
BA asymmetry	9 (40.9%)	78 (60.5%)	0.086 2.21; 0.88-5.56	NA
Suppression	5 (22.7%)	7 (5.4%)	**0.017** **5.13; 1.46-17.98**	0.390 2.02; 0.41-10.00
FSWA[k]	20 (90.9%)	114 (88.4%)	1.000 1.32; 0.26-6.20	NA
RSWA[l]	4 (19.0%)	22 (17.1%)	1.000 1.08;0.33-3.51	0.731 0.788; 0.20-3.06

1st EEG characteristics II (n=151)				
PD[m]	6 (28.6%)	21 (16.3%)	0.214, 1.93; 0.68-5.50	0.933 0.95; 0.27-3.34
IEA[n]	3 (13.6%)	13 (10.1%)	0.706 1.04; 0.367-5.41	NA

Legend to appendix O: [a]OR - odds ratio; [b]CI - confidence interval; [c]SD - standard deviation; [d]NIHSS – National Institutes of Health Stroke Scale score; [e]IQR -Interquartile range; [f]MCA - middle cerebral artery; [g]1st CT - 1st CT scan obtain at the emergency department; [h]ASPECTS - Alberta Stroke Program Early CT Score; [i]Cortical ASPECTS – value in ASPECTS considering only the 7 cortical territories of this scale; [j]BA - background activity; [k]FSWA - focal slow wave activity; [l]RSWA - rhythmic slow wave activity; [m]PD - periodic discharge; [n]IEA - interictal epileptiform activity; [o]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate; [p]Multivariate analysis - variables with a positive significant association in bivariate analysis, were adjusted for age, clinical stroke severity (admission NIHSS) and imaging infarct severity (ASPECTS), using a logistic regression model. The OR for age, NIHSS, and ASPECTS are derived from multivariable logistic models including exclusively these three variables, whereas the OR for the EEG variables are derived from models including age, NIHSS, ASPECTS and the respective EEG variables

From Project 9 (Quantitative EEG and outcome of ischaemic stroke patients)**:**

Appendix P. qEEG index calculations

Glossary:

RP – Relative Power;

AP – Absolute Power;

Affected – band power from electrodes in the affected ischaemic stroke hemisphere

Unaffected - band power electrodes in the unaffected hemisphere

D1 - EEG performed in the first 72 hours after stroke

D7 - EEG performed at day 7 after stroke or at discharge

Note: when not mentioned, power from all electrodes (affected, unaffected hemisphere and midline) was used.

QEEG indices:

I. GLOBAL RELATIVE **BAND** POWER INDICES

Delta RP = delta AP / (delta AP + theta AP + alpha AP + beta AP)

Theta RP = theta AP / (delta AP + theta AP + alpha AP + beta AP)

Alpha RP = alpha AP / (delta AP + theta AP + alpha AP + beta AP)

Beta RP = beta AP / (delta AP + theta AP + alpha AP + beta AP)

DTABR (Delta-theta / alpha-beta Ratio) = (delta AP + theta AP) / (alfa AP + beta AP)

DAR (delta AP / alpha AP ratio) = total delta AP / total alpha AP

II. SYMMETRY INDICES

BSI (brain symmetry index) = $\frac{1}{N}\sum_{i=1}^{N}\left\|\left(\frac{Ri-Li}{Ri+Li}\right)\right\|$; where: N = number of electrode pairs; R and L = AP in right and left hemisphere electrodes

Affected / Unaffected = affected hemisphere AP / unaffected hemisphere AP

III. AFFECTED and UNAFFECTED HEMISPHERE INDICES

Affected slow RP = (affected delta AP + affected theta AP) / (delta AP + theta AP)

Affected fast RP = (affected alpha AP + affected beta AP) / (alpha AP + beta AP)

Affected DTABR = (affected delta AP + affected theta AP) / (affected alpha AP + affected beta AP)

Unaffected DTABR = (unaffected delta AP + unaffected theta AP) / (unaffected alpha AP + unaffected beta AP)

Affected DAR = affected delta AP / affected alpha AP

Unaffected DAR = unaffected delta AP / unaffected alpha AP

IV. TIME CHANGES INDICES

Acute Symmetry Change Index = [(Affected AP in D1 – Unaffected AP in D1) – (Affected AP in D1 – Unaffected AP in D7] / [(Affected AP in D1 – Unaffected AP in D1) x (time between exams in days)]

Acute Delta Change Index = (delta AP in D1 – delta AP in D7) / [(delta AP in D1) x (time between exams in days)]

Acute Theta Change Index = (theta AP in D1 – theta AP in D7) / [(theta AP in D1) x (time between exams in days)]

Acute Alpha Change Index = (alpha AP in D1 – alpha AP in D7) / [(alpha AP in D1) x (time between exams in days)]

Acute Beta Change Index = (beta AP in D1 – beta AP in D7) / [(beta AP in D1) x (time between exams in days)]

Acute DTABR Change Index = (DTABR in D1 – DTABR in D7) / [(DTABR in D1) x (time between exams in days)]

From Project 9:

Appendix Q.

Appendix Q.1. – Symmetry and affected/unaffected qEEG indices and outcome at discharge.

qEEG Index	mRS<3	mRS≥3	Bivariate analysis (p)	Multivariate analysis OR (95%CI)	Cross-validated AUC (95% CI)
1st EEG (0-72h)					
BSI	0.13 ± 0.06 (0.13)	0.16 ±0.07 (0.15)	0.010	ns	NA
Affected AP / unaffected AP	1.22 ± 0.35 (0.12)	1.37 ± 0.46 (1.25)	ns	NA	NA
Affected slow RP	0.49 ± 0.08 (0.48)	0.52 ± 0.09 (0.52)	ns	NA	NA
Affected fast RP	0.44 ± 0.05 (0.44)	0.41 ± 0.06 (0.41)	0.003	ns	NA
Affected DTABR	1.89 ± 1.64 (1.38)	5.07 ± 4.17 (3.97)	<0.001	2.74 (1.62-4.64); p<0.001	0.815 (0.744 - 0.885)
Affected DAR	3.00 ± 3.23 (2.08)	8.90 ± 9.27 (6.09)	<0.001	2.44 (1.57-3.79); p<0.001	0.821 (0.751 - 0.891)
Unaffected DTABR	1.58 ± 1.15 (1.34)	3.63 ± 3.01 (2.80)	<0.001	3.03 (1.66-5.51); p<0.001	0.814 (0.743 - 0.885)
Unaffected DAR	2.34 ± 2.45 (1.66)	4.99 ± 4.73 (3.44)	<0.001	2.30 (3.70); p<0.001	0.794 (0.719 - 0.870)

Legend to appendix Q1: Results in the 2nd and 3rd column are shown as mean ± standard deviation (median) of the natural logarithm of the EEG index. Multivariate analyses included the variables age, NIHSS score at admission and ASPECTS; OR - odds ratio; CI 95% - 95% confidence interval; RP - relative power; affected - affected ischaemic stroke hemisphere; unaffected - unaffected hemisphere; slow - delta + theta; fast - alpha + beta; DTABR - delta-theta to alpha-beta ratio; DAR - delta to alpha ratio; ns - non-significant; NA - not applicable. All bivariate analysis were performed with Mann-Whitney U test.

Appendix Q.2. Symmetry, affected and unaffected and time changes qEEG indices and outcome at 12 months.

qEEG Index	mRS<3	mRS≥3	Bivariate analysis (p)	Multivariate analysis OR (95%CI)	Cross-validated AUC (95% CI)
1st EEG (0 – 72 hours)					
BSI	0.14 ± 0.06 (0.13)	0.17 ± 0.08 (0.15)	0.008	ns	-
Affected AP/unaffected AP	1.27 ± 0.34 (1.18)	1.37 ± 0.50 (1.25)	ns	-	-
Affected fast RP	0.43 ± 0.05 (0.44)	0.41 ± 0.07 (0.41)	0.002*	ns	-
Affected slow RP	2.37 ± 2.12 (1.69)	5.56 ± 4.39 (4.48)	ns*	-	-
Affected DTABR	2.36 ± 2.12 (1.69)	5.56 ± 4.39 (4.48)	<0.001	2.67 (1.56-4.55) p<0.001	0.831 (0.766 - 0.896)
Affected DAR	3.58 ± 3.40 (2.48)	10.09 ± 10.07 (7.74)	<0.001	2.55 (1.59-4.08) p<0.001	0.849 (0.788 - 0.911)
Unaffected DTABR	1.74 ± 1.14 (1.48)	4.08 ± 3.24 (3.16)	<0.001	3.62 (1.88-7.02) p<0.001	0.852 (0.791 - 0.913)
Unaffected DAR	2.38 ± 2.00 (2.22)	5.74 ± 5.15 (4.20)	<0.001	2.62 (1.56-4.41) p<0.001	0.850 (0.787 - 0.912)
2nd EEG (day 7 / discharge)					
BSI	0.13 ± 0.06 (0.11)	0.16 ± 0.07 (0.14)	0.002	ns[b]	-
Affected/unaffected	0.49 ± 0.07 (0.48)	0.48 ± 0.08 (0.47)	ns	-	-
Affected fast RP	0.42 ± 0.04 (0.43)	0.39 ± 0.07 (0.39)	<0.001*	0.02 (0.001-0.45) p=0.014	0.789 (0.715 - 0.864)
Affected slow RP	0.49 ± 0.07 (0.48)	0.48 ± 0.08 (0.47)	<0.001*	0.39 (0.01-5.25) p<0.001	0.776 (0.699 - 0.852)
Affected DTABR	2.39 ± 2.84 (1.46)	13.31 ± 48.01 (5.83)	<0.001	2.76 (1.7-4.47) p<0.001	0.838 (0.771 - 0.904)
Affected DAR	3.15 ± 3.83 (1.74)	21.11 ± 78.78 (8.39)	<0.001	2.32 (1.54-3.48); p<0.001	0.833 (0.766 - 0.899)
Unaffected DTABR	1.49 ± 1.31 (1.06)	8.67 ± 26.26 (3.05)	<0.001	3.45 (1.9-6.15); p<0.001	0.836 (0.771 - 0.901)
Unaffected DAR	2.04 ± 1.97 (1.28)	13.40 ± 42.80 (4.11)	<0.001	2.58 (1.61-4.15); p<0.001	0.832 (0.766 - 0.898)
qEEG Index	**mRS<3**	**mRS≥3**	**Bivariate analysis (p)**	**Multivariate analysis OR (95%CI)**	**Cross-validated AUC**

					(95% CI)
Time Changes índices					
Acute Symmetry Change Index	-0.22 ± 1.07 (0.04)	-0.22 ±1.03 (0.08)	ns	NA	NA
Acute Delta Change Index	-0.16 ± 1.04 (0.05)	-0.48 ± 2.05 (0.05)	ns	NA	NA
Acute Alpha Change Index	-0.71 ± 3.47 (-0.01)	-0.34 ± 1.25 (0.02)	ns	NA	NA
Acute Beta Change Index	-0.97 ± 3.68 (0.01)	-0.64 ± 3.38 (0.05)	ns	NA	NA
Acute DTABR Change Index	0.03 ± 0.11 (0.05)	-0.29 ±1.42 (0.002	0.008	ns	NA

Legend to appendix Q2: Results in the 2nd and 3rd column are shown as mean ± standard deviation (median) of the natural logarithm of the EEG index. Multivariate analyses included the variables age, NIHSS at admission and ASPECTS scores; slow - delta + theta; fast - alpha + beta; DTABR - delta-theta to alpha-beta ratio; DAR - delta to alpha ratio; OR - odds ratio; RP – relative power; ns - non-significant; NA - not applicable. *t-test (otherwise Mann-Whitney U test)

XVII. *FACSIMILE*

"I love science…
Show me the research, show me the results, show me the conclusions –
and then show me some qualified peer reviews of all that"
Claire Scovell LaZebnik

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Usefulness of EEG for the differential diagnosis of possible transient ischemic attack ☆

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ABSTRACT

Objective: EEG value in possible transient ischemic attacks (TIA) is unknown. We aim to quantify focal slow wave activity (FSWA) and epileptiform activity (EA) frequency in possible TIA, and to analyse its contribution to the final diagnosis of seizures and/or definitive TIA.
Methods: Prospective longitudinal study of possible TIA patients evaluated at a tertiary centre during 36 months and with 1–3 months follow-up. EEG was performed as soon as possible (early EEG) and one month later (late EEG). A stroke neurologist established final diagnosis after reassessing all clinical and diagnostic tests.
Results: 80 patients underwent an early EEG (45.8 h after possible TIA): 52 had FSWA and 6 of them also EA. Early FSWA was associated with epileptic seizure or definitive TIA final diagnosis ($p = .041$). Patients with these diagnoses had more frequently early FSWA (19/23; 82.6%) than EA (6/23; 26.1%). 6/13 (46.2%) patients with epileptic seizure final diagnosis had EA.
Results: In the late EEG, 43 (58.1%) patients demonstrated persistent FSWA and 3 of them also EA. Persistent FSWA in the late EEG was more frequent in seizures than in TIA patients (91.7% vs. 45.5%). FSWA disappearance was associated with acute vascular lesion on neuroimage.
Conclusions: FSWA was the commonest EEG abnormality found in the early EEG of patients with possible TIA, but did not distinguish between TIA and seizure patients. In patients with seizures, FSWA was more common than EA and its presence in the late EEG was more likely in patients with epileptic seizures than with TIA.
Significance: The majority of possible TIA patients with the final diagnosis of epileptic seizures do not have EA in the early or late EEG.

1. Introduction

Neurological syndromes lasting less than 24 h include not only Transient Ischemic Attacks (TIA) but also other clinical entities such as epileptic seizures. The differential diagnosis between a transient ischaemic attack (TIA), an epileptic seizure or other transient neurological disturbances can be challenging and depends on the clinician's expertise (Calanchini et al., 1977; Castle et al., 2010; Ferro et al., 1996; Fonseca and Canhão, 2011; Kraaijeveld et al., 1984; Prabhakaran et al., 2008) and also on the available clinical information (Beniczky et al., 2012; Deacon et al., 2003; Fonseca and Canhão, 2011; Jin et al., 2014; Prabhakaran et al., 2008).

After extensive clinical investigation, approximately one-fourth of TIA patients are only labelled as "probable" or "possible TIA" (Fonseca and Canhão, 2011; Prabhakaran et al., 2008), defined as a clinical syndrome lasting less than 24 h that do not fulfil accepted criteria for TIA nor for another diagnosis, although a vascular origin cannot be excluded (Correia et al., 2015; Fonseca and Canhão, 2011). The main reasons for classification difficulties of possible TIA include odd accompanying symptoms (such as prickles/itching

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sensations, rigid postures or movement of the limbs), march of symptoms, consciousness disturbance or amnesia with focal symptoms, multiple stereotyped episodes, positive visual phenomena, isolated speech disturbance/confusion and focal symptoms plus panic or anxiety and paucity of details in the symptoms description (Fonseca and Canhão, 2011).

Diagnostic challenges between a TIA and an epileptic seizure include non-convulsive and inhibitory or negative seizures (Fisher, 1978; Kaplan, 1993; Lee and Lerner, 1990; Primavera et al., 1993) and TIA with positive symptoms, such as "limb-shaking" TIA (Fisher, 1962; Muraga, 2016). Further hampering this distinction is the possibility of epileptic seizures caused by a TIA (Cocito and Loeb, 1989; Ferracci et al., 2000; Primavera et al., 1993) and the existence of other mimics with a non-vascular and non-epileptic origin (Carreño, 2008).

De Reuck and Van Maele (De Reuck and Van Maele, 2009) analysed the role of EEG in the differential diagnosis of a TIA versus an inhibitory seizure and concluded that an early EEG is crucial in their investigation. However, the type and frequency of electroencephalographic abnormalities in possible TIA and its value in the distinction between epileptic seizures and TIA is not exactly known. In this study we aim to respond to the following:

1) What is the frequency of electroencephalographic abnormalities in patients with possible TIA and to which clinical/imaging characteristics are they associated?
2) What is the percentage of patients with possible TIA with a final diagnosis of epileptic seizure or definitive TIA and which electroencephalographic characteristics differentiate these diagnoses?

2. Methods

Prospective longitudinal study of patients with a diagnosis of possible TIA evaluated at the TIA Clinic or admitted to the Stroke Unit of the Hospital de Santa Maria (HSM-CHLN), between November 2010 and October 2013. The Ethics Committee *"Comissão de Ética para a Saúde"* of the HSM-CHLN approved this study.

As inclusion criteria, the patients had to meet the clinical criteria for an initial diagnosis of possible TIA (see definition below) and gave their informed consent. Symptoms suggestive of brainstem/cerebellum involvement were exclusion criteria. The study design is described in Fig. 1.

2.1. Standardized clinical and ancillary evaluation (Correia et al., 2015; Fonseca and Canhão, 2011)

Patients were referred to the TIA Clinic by the HSM-CHLN emergency department (ED) or their family doctor. In the ED, patients underwent routine blood tests, ECG and brain non-contrast CT scan (CT) and were prescribed with antiplatelet agents and statins. In the daily TIA Clinic, a stroke neurologist performed a structured clinical interview and physical and neurological examination. On the same day, patients underwent carotid and vertebral duplex scans, transcranial Doppler and blood tests. Transthoracic or transesophageal echocardiography or 24 h Holter were ordered, whenever considered necessary. When possible, an MRI including diffusion-weighted imaging (DWI) was done. A neuroradiologist reported all imaging exams. The stroke neurologist, after review of all exams, decided about further treatment, the need for hospitalization and booked the patient for a follow-up appointment one to three months later.

Patients with a possible TIA were admitted to the Stroke Unit, from the ED or TIA Clinic, whenever a definitive diagnosis of TIA was not established, symptoms had not cleared or the patient was judged to be at a high risk of recurrence. The evaluation of admitted patients and their follow-up was similar to those in the TIA Clinic.

The following symptoms associated with possible TIA were systematically recorded: motor, sensory, speech disturbances, partial

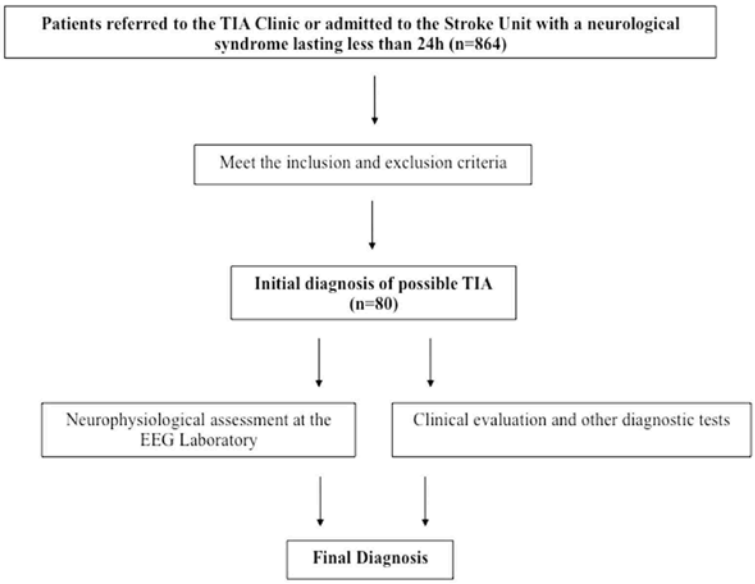

Fig. 1. Study Design. TNA – Transient Neurological Attack/TIA – Transient Ischaemic Attack.

or total amnesia for the event, consciousness disturbance, and confusional period. Positive symptoms were defined as the occurrence of involuntary movements, sensory symptoms apart from numbness or anaesthesia (such as tingling, stinging, prickling, burning sensations or pain) and visual delusions (palinopsia, polyopia, micro, macro or metaphormopsia), simple (e.g.: lights, spots, oscillating lines with bright, sparkle or colour) or complex hallucinations. The presence of a Jacksonian march of symptoms was considered whenever there was sequential spread of motor (or sensory) symptoms beginning at a specific body region to involve other body parts, accordingly to an electrical disturbance spreading through the homunculus of the motor (or sensory) cortex (Larner, 2011)

Patients were classified in 5 symptomatic groups, not mutually exclusive, taking into account symptom characteristics and their different specificity for the final diagnosis:

1. Motor symptoms
2. Positive phenomena and/or march of symptoms (more frequent in seizures than in TIA)
3. Sensory and/or visual symptoms (posterior brain symptoms)
4. Speech disturbance
5. Amnesia for the event and/or consciousness disturbance and/or confusional period (including consciousness, level or content, disturbance symptoms)

2.2. Diagnostic criteria

The diagnosis of each patient was defined according to the following criteria:

- *Initial diagnosis*: established at the end of the first observation in TIA Clinic or Stroke Unit by a stroke neurologist (PC).
- Final diagnosis: established after the end of the study by a stroke neurologist (PC), taking into account clinical reassessment 1–3 month after the clinical episode, and the result of all diagnostic tests (including early and late EEG). Patients were reclassified in the following final diagnosis groups: TIA; possible TIA; epileptic seizures; other TIA mimic (including migraine; psychiatric disturbance; others). Another neurologist trained in epilepsy (CB), having had access to the same clinical and complementary information, independently reclassified the patients in the same final diagnosis groups.

The following definitions were used for the diagnosis (initial and final):

- Transient ischaemic attack (*TIA*): Clinical syndrome characterized by sudden focal neurological symptoms, presumed to be of vascular origin, that lasted less than 24 h (WHO, 1975), regardless of whether or not brain imaging showed a recent ischaemic lesion. This diagnosis group included patients with an acute onset of temporary (less than 24 h) neurological dysfunction consistent with focal brain ischemia and with supportive or no contradictory complementary diagnostic tests including brain imaging demonstrating or not an acute vascular ischemic lesion. The typical history for a TIA was a swift onset (no symptoms to maximal symptoms in less than five minutes) of a motor defect, sensory defect, aphasia, loss of vision in one eye or in part of one eye, homonymous hemianopia, or a combination of the above (WHO, 1975). In these patients an epileptic seizure or another TIA mimic did not cause the clinical syndrome.
- Possible transient ischaemic attack (*possible TIA*): Neurological syndrome lasting less than 24 h that do not fulfil international accepted criteria for TIA nor the criteria for a specific mimic diagnosis, although a vascular origin could not be excluded (Correia et al., 2015; Fonseca and Canhão, 2011). This diagnosis group included patients with odd accompanying symptoms (such as prickles/itching sensations, rigid postures or movement of the limbs), march of symptoms, consciousness disturbance or amnesia with focal symptoms, multiple stereotyped episodes, positive visual phenomena, isolated speech disturbance/confusion and focal symptoms plus panic or anxiety and paucity of details in the symptoms description, (Fonseca and Canhão, 2011) without imaging/laboratory evidence of ischemic cerebral pathology (Kidwell and Warach, 2003) nor of another TIA mimic.
- Transient ischaemic attack mimic (*TIA mimic*): Focal neurological syndrome lasting less than 24 h, for which a non-vascular cause was definitively established according to predefined criteria (Fonseca and Canhão, 2011) (e.g.: migraine with aura) (Headache Classification Subcommittee of the International Headache Society, 2004), metabolic syndrome, transient global amnesia (Caplan, 1985; Hodges and Warlow, 1990), panic attack (American Psychiatric Association, 2000), somatoform disorder (American Psychiatric ssociation, 2000). An epileptic seizure can also be a TIA mimic but was classified separately in this study.
- Epileptic seizure (*seizure*): transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain (Fisher et al., 2014). This diagnosis group included patients with positive motor, sensitive, or sensorial symptoms (as previously described) and also with motionless, unresponsive or automatic behaviour according to stereotyped focal seizures and/or successful response to antiepileptic treatment, epileptiform activity on EEG (D'Ambrosio and Miller, 2010) or the occurrence of an unequivocal seizure in the follow-up. In these patients a TIA and a TIA mimic have been excluded. Accordingly, in patients with possible TIA, the final diagnosis of seizure was established (if other diagnoses were considered excluded after all diagnostic tests and clinical reassessment) in two different circumstances: 1) in patients with possible seizure semiology and epileptiform activity in the EEG; 2) in patients with possible seizure semiology and no epileptiform activity in the EEG but with additional (or better described) clinical events clearly indicative of seizures during the follow-up.

TIA and epileptic seizures were considered the two final diagnoses of interest for this study.

2.3. Neurophysiological assessment

All patients underwent a 64-channel video-EEG using a digital Nihon-Kohden device and electrodes placed in accordance with the international 10/10 system and following national and international recommendations (American Clinical Neurophysiology Society, 2006a,b; Flink et al., 2002; Martins da Silva et al., 2011; Nuwer et al., 1998) in two different periods: 1) As soon as possible after the possible TIA (*early EEG*); 2) One month after (*late EEG*). We intend to repeat EEG, based on guidelines reporting that repeating EEG may be helpful when the diagnosis of epilepsy is unclear (National Institute for Health and Care Excelence, (NICE), 2012)). One month after the clinical event was the date chosen for EEG repetition to match the scheduled follow-up clinical visit.

The record had a maximum duration of 60 min, including an eye closed wake resting condition and eye open, hyperventilation and photic stimulation manoeuvres.

Two clinical neurophysiologists (CB + RP), blinded for the final diagnosis, interpreted the records. Discrepancies were decided by consensus. All EEG records were evaluated for the presence of

the following abnormalities: background activity slowing (Noachtar et al., 1999); asymmetry (Hirsch et al., 2013); suppression (focal, hemispheric or diffuse) (Hirsch et al., 2013); focal slow wave activity (including focal and regional concept) (Noachtar et al., 1999); epileptiform activity (Noachtar et al., 1999), periodic discharges (Hirsch et al., 2013) and others.

The two EEG variables of interest for the present study were *Focal Slow Wave Activity (FSWA)* and *Epileptiform Activity (EA)* (Fig. 2). The following operational definitions were used:

- *FSWA:* continuous or intermittent slow activity i.e. theta and/or delta band activity (Noachtar et al., 1999) limited to an area of the brain or scalp region (includes the concept of focal and regional (Noachtar et al., 1999)).
- *EA:* (Noachtar et al., 1999): transients clearly distinguishable from background activity, with a characteristic spiky morphology at a conventional time scale, duration of 70–200 ms (sharp wave) or from 20 to under 70 ms (spike) and a main component generally negative relative to other areas.

FSWA evolution between early and late EEG was also analysed and considered "*persistent*" if existing in both exams (even if intermittently), "*transient*" if present in the early but absent in the late and "*absent*" if non-existent in both EEG.

2.4. Statistics

Univariate descriptive statistics were used for categorical and continuous variables. Bivariate analysis was performed using χ^2 test, Fisher's exact test or t-student or Mann-Whitney test, as appropriate. The level of significance was established at $\alpha < 0.05$ (two-tailed).

To define independent predictors of neurophysiological outcomes, significant variables at $p < .05$ in the bivariate analysis were tested in multivariate analysis using a stepwise binomial logistic regression with backward elimination. A Hosmer and Lemeshow test assessed the calibration of the model and the Receiver Operator Characteristic (ROC) curve its discriminative capacity.

As a measure of final diagnosis interobserver agreement we used Cohen's kappa statistic.

The statistical analysis was performed using SPSS software version 21 for Mac.

3. Results

Eighty patients were included with the initial diagnosis of possible TIA. Table 1 describes the demographic, clinical, imaging and electroencephalographic characteristics of these patients.

3.1. Frequency of EEG abnormalities

In the early EEG, 52/80 patients (65%) had FSWA, 6 of them also EA (6/80 7.5%) and 7/80 (11.7%) other abnormalities (increase of beta activity in 5 and diffuse slowing of background activity in 2). The EEG record was reported as normal in 21/80 patients (26.2%).

After one month, 74 patients (92.5%) repeated the EEG, which was normal in 25 (33.8%). In this record, 44/74 (59.5%) patients had FSWA. FSWA evolution (Table 1) was demonstrated persistent in 43 (58.1%), transient in 6 (8.1%) and absent in 24 (32.4%) patients. In one patient (1.4%), FSWA only emerged in the late EEG. Only 3 of the 6 patients with EA in the early EEG retained this activity in the late EEG. No patient showed EA in this exam when not present in the early EEG.

At the time of the early EEG (Supplementary file 1), 11 patients (13.8%) were being treated with antiepileptic drugs (AED). During follow-up, 7 patients (3 with EA in early EEG) were prescribed AED (6 for epileptic seizures and 1 for migraine). At the time of the late EEG, 18 patients (24.3%) were on AED.

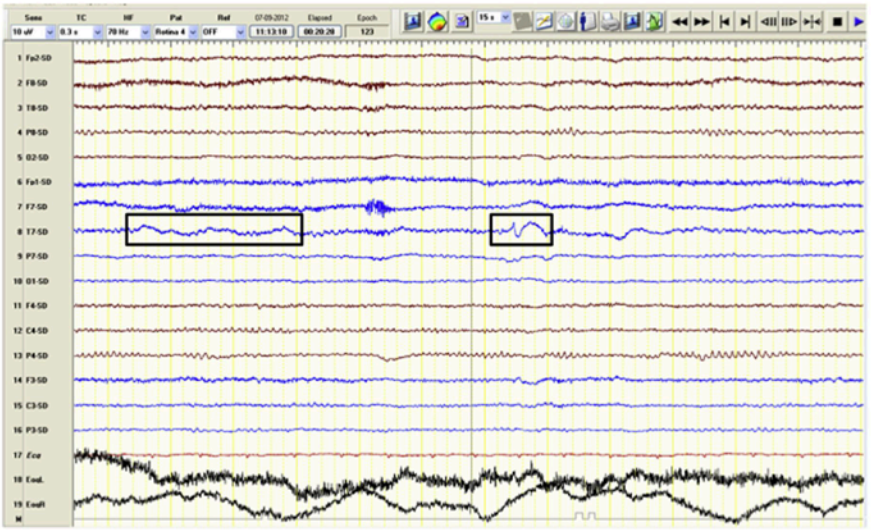

Fig. 2. Focal Slow Wave Activity and Epileptiform activity. Source derivation montage of a 15 mm/s EEG page. Left Black Square highlights Focal Slow Wave Activity and right Black Square identifies Epileptiform Activity (abrupt wave followed by a slow wave).

Table 1
Demographic, clinical, imaging and electroencephalographic characteristics of patients with the initial diagnosis of possible TIA.

Demographic characteristics		
Male/Female	36/44 (45%/55%)	
Age (Years)	Mean: 65.5 (S.D. 14.4); Median: 68.5	
Clinical characteristics		
Sudden onset (<1 min)	54 (71.1%)	
Motor symptoms	20 (25%)	
Positive symptoms and/or March of symptoms	40 (50%)	
Sensory symptoms and/or visual symptoms	43 (53.8%)	
Speech disturbance	43 (53.8%)	
Amnesia and/or consciousness disturbance and/or confusional period	36 (45%)	
Number of previous episodes	Mean: 2.1 (S.D. 1.3); Median: 2	
Mean duration of the last episode (hours)	Mean: 2.4 (S.D. 4.8); Median = 0.5	
Time between symptoms and EEG (hours)	Mean: 45.8 (S.D. 37.5); Median: 37.5	
Imaging characteristics		
MRI (n = 43/53.8%)	DWI+	4 (9.3%)
	Another lesion	22 (51.2%)
Electroencephalographic characteristics		
Early EEG (n = 80)	FSWA	52 (65%)
	EA	6 (7.5%)
Late EEG (FSWA evolution; n = 73/91.2%)	Persistent FSWA	43 (58.9%)
	Absent or transient FSWA	30 (41.1%)

EA – Epileptiform Activity, FSWA – Focal Slow Wave Activity, DWI+ – acute vascular lesion on MR diffusion-weighted imaging, S.D. – Standard deviation.

3.2. Clinical/Imaging characteristics associated with EEG abnormalities

3.2.1. Age

Both patients with FSWA in the early EEG and patients with demonstrated persistent FSWA in the late EEG were respectively 12.3 ± 3.4 ($t(43.43) = 3.63$, $p = .001$) and 11.3 ± 3.1 years ($t(46.52) = 3.66$, $p = .001$) older than the remaining sample.

There was no significant difference in the mean age of patients with or without EA in the EEG ($t(78) = -1.17$, $p = .902$).

3.2.2. Neurological syndrome characteristics

No significant associations were found between the variables of the two EEG and the number of previous episodes, duration or the time interval between the clinical event and the EEG.

The electroencephalographic characteristics of the different symptomatic groups under study are depicted in Table 2.

In the early EEG, FSWA was associated with amnesia for the event and/or consciousness disturbance and/or a confusional period (Table 2). In this exam, 5 patients with EA (83%) had a clinical syndrome with speech disturbances and 4 (66.7%) at least one of the following: amnesia for the event, consciousness disturbance and/or confusional period. EA was significant associated with a neurological syndrome with consciousness disturbance (Fisher's exact test, $p = .040$, OR = 6.59, 95% CI: 1.11–39.15).

In the late EEG, persistent FSWA was associated with the presence of speech disturbances ($\chi^2 = 7,41$, $p = .006$, OR = 3.77, 95% CI: 1.42–9.97) and transient FSWA with a confusional period (Fisher's exact test, $p = .047$, OR = 6,25, 95% CI: 1.04–37.37).

In a binomial logistic regression model, FSWA was no longer predicted ($p = .499$, OR = 1.47, 95% CI: 1.02–1.11) by "amnesia and/or consciousness disturbance and/or confusional period" when adjusted for age ($\chi^2(2) = 14.00$, $p < .0005$; Nagelkerke$R^2 = 22.1\%$; Hosmer-Lemeshow test, $p = .839$; AUC = 0.74, $p < .0005$, 95% CI: 0.62–0.87).

Persistent FSWA in the late EEG was independent predicted by both age ($p = .002$, OR = 1,08, 95% CI: 1.03–1.13) and "speech disturbances" ($p = .02$, OR = 3.54, 95% CI: 1.22–10.28) in the logistic regression model ($\chi^2(1) = 17.73$, $p < .0005$; Nagelkerke$R^2 = 31.4\%$; Hosmer-Lemeshow test, $p = .714$; AUC 0.80; $p < .0005$, 95% CI: 0.69–0.90).

3.2.3. Imaging characteristics

No differences in EEG variables were observed in patients with and without normal MRI. Among patients with an acute vascular lesion in the MRI (DWI+), three (75%) had FSWA in the early EEG and in two of them (66.7%) this activity disappeared in the late EEG (Fisher's exact test, $p = .011$).

3.3. Final diagnosis of epileptic seizure or definitive TIA in patients with possible TIA

After all diagnostic tests and clinical reassessment, patients with possible TIA were reclassified in a final diagnosis (Fig. 3).

Thirteen patients were diagnosed with epileptic seizures (16.3%) and 11 (13.8%) with definitive TIA by the stroke neurologist (PC). One patient had a final dual diagnosis of definitive TIA and epileptic seizures. This patient was discharged from the Stroke Unit with a TIA diagnosis. However, in the follow-up appointment the patient reported different episodes that were then diagnosed as partial complex seizures.

3.3.1. Interobserver agreement

The two neurologists agreed in the diagnosis of 59 patients (73.8%). The interobserver concordance in the final diagnosis was good ($k = 0.627$, $p < .0005$, 95% CI: 0.485–0.769). In the analysis of the diagnosis of seizure (vs. non-seizure), the two classifiers agreed in 73 patients (91.2%). The interobserver agreement was good ($k = 0.707$, $p < .0005$, 95% CI: 0.503–0.911). Also, for the diagnosis of definitive TIA (vs. non definitive TIA) the interobserver agreement was good ($k = 0.789$, $p < .0005$, 95% CI: 0.587–0.991), with a concordant diagnosis in 76 patients (95%).

3.3.2. Clinical/Imaging characteristics associated with the final diagnosis of interest

No significantly mean age difference was found between patients with final diagnosis of epileptic seizures or TIA and other final diagnosis ($t(65.85) = 1.474$, $p = .145$).

Clinical and EEG characteristics of patients with the final diagnosis of seizures and definitive TIA are displayed inTable 3.

Of the evaluated symptoms, only the existence of a Jacksonian March of symptoms was more frequent in seizure patients (n = 7;

Table 2
Electroencephalographic abnormalities in different symptomatic groups.

Type of Symptoms*	Motor		Positive and/or March of symptoms		Sensory and/or Visual		Speech disturbances		Amnesia and/or Impaired consciousness and/or Confusional period	
Early EEG (n = 80/100%)	n = 20		n = 40		n = 43		n = 43		n = 36	
	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	N	p, OR, 95% CI
FSWA (n = 52)	12	.588, 0.750, 0.26–2.13	24	.348, 0.64, 0.26–1.62	23	**.020, 0.320, 0.12–0.85**	32	.057, 2.47, 0.96–6.34	28	**.030, 2.92, 1.09–7.81**
EA (n = 6)	3	.162, 3.35, 0.62–18.16	2	.675, 0.47, 0.08–2.75	0	**.008, RR = 0.42, 0.32–0.55**	5	.209, 4.74, 0.53–42.53	4	.401, 2.62, 0.45–15.24
Late EEG (FSWA evolution; n = 73/91.2%)	n = 18		n = 37		n = 39		n = 40		n = 34	
	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI
Persistent FSWA (n = 43)	10	.739, 0.83, 0.28–2.44	20	.393, 0.67, 0.26–1.70	16	**.001, 0.18, 0.06–0.51**	29	**.009, 3.58, 1.34–9.52**	23	.156, 1.99, 0.76–5.16
Absent or transient FSWA (n = 30)	8		17		23		11		11	

EA – Epileptiform Activity, FSWA – Focal Slow Wave Activity.
Bold values represent $p < 0.05$.
* The different symptomatic groups are not mutually exclusive. The bivariate statistical analysis was performed using $\chi 2$ test or Fisher's exact test having as independent variable each symptomatic group and as dependent variable each EEG characteristic.

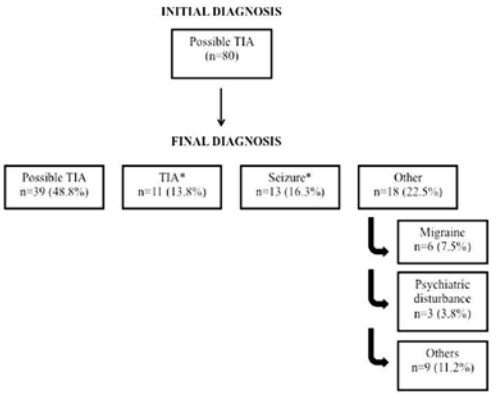

Fig. 3. Reclassification of possible TIA. *A patient classified as TIA had the concomitant diagnosis of epileptic seizures (partial complex seizures) in the clinical follow-up.

50%) than in patients with definitive TIA (n = 1; 9.1%) (Fisher's exact test, p = .027, OR = 14.000, 95% CI: 1.329–147.429).

MRI was performed on eight (66.7%) patients with epileptic seizures and five (45.4%) patients with the final diagnosis of definitive TIA, four of whom (80%) had an acute vascular lesion in the DWI.

3.4. Electroencephalographic characteristics in patients with epileptic seizure and definitive TIA diagnosis

FSWA in the early EEG was differently distributed between final diagnosis groups (p = .027). Furthermore, FSWA in the early EEG was associated with the final diagnosis of epileptic seizure or definitive TIA compared to other type of final diagnosis (19/23 patients versus 33/57 patients; p = .041; OR 3.46; 95% CI 1.04–11.46).

The only significant EEG difference between patients with epileptic seizures and definitive TIA was a different evolution of FSWA between the early and the late EEG (Table 3). The chance of persistent FSWA in the late EEG was significantly greater (13.2 times higher) in a patient with an epileptic seizure than in a patient with TIA. In fact, the majority of patients with seizures (91.7%) maintained the FSWA between the two examinations while the same only occurred in less than half (45.5%) of TIA patients. Furthermore, absent or transitory FSWA was less frequent in patients with seizures (8.3%) than with TIA (54.5%).

Although a higher percentage of patients with epileptic seizures had EA, this difference was not statistically significant. Of the 13 patients who had the final diagnosis of epileptic seizures, six (46.2%) had EA in the early EEG.

4. Discussion

FSWA was the commonest EEG abnormality found in the early EEG of patients with possible TIA, but did not distinguish between TIA and seizure patients. In patients with seizures, FSWA was more common than epileptiform activity and its presence in the EEG one month later was more likely in patients with epileptic seizures.

In this work, EEG abnormalities were frequent, occurring in 73.8% of the patients. FSWA was the most common, although others could be identified. This percentage is similar to that found by De Reuck and Van Maele (2009) in patients with inhibitory seizures (76%), but rather different from that of patients with defini-

Table 3
Clinical characteristics of the patients with a final diagnosis of seizures and TIA.

	Final diagnosis			p
	Seizures* (n = 12)	TIA* (n = 11)		
Age in years (SD)	68.2 (10.4)	68.9 (9.1)		.874
Total duration of symptoms in hours (SD)	1.3 (1.5)	1.8 (2.6)		.695
Number of previous episodes (SD)	2.8 (1.8)	2.4 (1.6)		.874
Time between symptoms and EEG in hours (SD)	34.6 (32.3)	38.2 (26.1)		.561
Symptoms				p, OR, 95% CI
Motor symptoms	4 (33.3%)	6 (54.5%)		.414 0.417, 0.08–2.25
Positive symptoms and/or March of symptoms	7 (58.3%)	3 (27.3%)		.214 3.73, 0.65–21.58
Sensory and/or visual symptoms	3 (25%)	5 (45.4%)		.400 0.40, 0.07–2.34
Speech disturbances	8 (66.7%)	8 (72.7%)		1.000 0.75, 0.12–4.49
Amnesia and/or Consciousness disturbance and/or Confusional period	7 (58.3%)	5 (45.4%)		.537 1.68, 0.32–8.76
Electroencephalographic characteristics				
Early EEG	FSWA	11 (91.7%)	8 (72.7%)	.317 4.12, 0.36–47.30
	EA	5 (41.7%)	1 (9.1%)	.1557.14, 0.68–75.22
Late EEG (FSWA evolution)	Persistent FSWA	11 (91.7%)	5 (45.4%)	.027 13.20, 1.24–140.68
	Absent or transient FSWA	1 (8.3%)	6 (54.5%)	

EA – Epileptiform Activity, FSWA – Focal Slow Wave Activity, TIA – Transient Ischaemic Attack.
* The patient who had the final dual diagnosis of TIA and seizures is included in this table only in the TIA group because the clinical episode that provoked the admission to the Stroke Unit had the final diagnosis of TIA.

tive TIA (7.6%) in the same study. Unlike this Belgian study, we did not recognise early EEG differences between epileptic seizure and definitive TIA patients. There are some plausible explanations for this apparent discrepancy between the two studies, namely time until EEG and age. Neurological syndromes lasting less than 24 h are, by definition, time-limited events of neurological dysfunction and, for that reason, time interval between clinical manifestations and EEG might influence the presence or the type of electroencephalographic abnormalities. In the De Reuch and Van Maele study, 100% of patients with seizures but less than half of patients with definitive TIA underwent an EEG in the first 24 h. Furthermore, temporal slowing is a frequent finding in older patients (Samson-Dollfus et al., 1991) and seizure patients were older than TIA patients in the same study. In our series, time until EEG and age were not significantly different in patients with seizures and with TIA.

In this series of possible TIA patients, epileptic seizures were the most common final diagnosis, followed by definitive TIA. Approximately one half of the patients remained undiagnosed, clearly showing the differential diagnosis difficulty of possible TIA and the need for complementary strategies supporting the classification of these undefined events (Dolmans et al., 2015). Sequential spread of symptoms according to the homunculus of the motor (or sensory) cortex were associated with the diagnosis of epileptic seizures, in agreement with the "Jacksonian march" characteristic of focal seizures (York and Steinberg, 2011).

In our work, patients with early FSWA had a higher probability of subsequent diagnosis of epileptic seizures or definitive TIA, not explained by a different mean age between final diagnosis groups. Furthermore, a higher percentage of patients with these final diagnoses had early FSWA compared to early EA (82.6% vs. 26.1%, respectively). Although FSWA is not specific to the final diagnosis, it was informative and more sensitive than EA. In line with these results, a patient with a possible TIA with early FSWA should be further investigated and followed-up.

Six patients (7.5%) had EA in the early EEG, a higher percentage than the reported frequency of false-positive (0.5–1%) in asymptomatic individuals (Gregory et al., 1993; Robin et al., 1978). The percentage of patients with a definite diagnosis of epileptic seizures and EA in the early EEG (46.2%) is within the range of sensitivity reported for EEG (26 to 56%) as a diagnosis test for epilepsy (National Institute for Health and Care Excelence, (NICE), 2012). Still, it is possible that AED prescription in 14% of the patients reduced the probability of finding EA in the early EEG (Jawad et al., 1986; Milligan et al., 1982; Pro et al., 2009; Rocamora et al., 2006). Furthermore, focal seizures arising from small foci or deep foci for the recording electrodes may not have a surface EEG correlate. It is known that the repetition of EEG can be useful when the diagnosis of epilepsy is not clear (National Institute for Health and Care Excelence, (NICE), 2012; Scottish Intercollegiate Guidelines Network, 2015). Salinsky and collaborators (Salinsky et al., 1987) showed that 50% of epilepsy patients had EA in the first EEG, 84% in the third EEG and 92% in the fourth EEG. However, in our study, the repetition of the EEG did not improve the EEG value in EA detection, as would be expected. There are two possible reasons for this finding. On the one hand, there is the already discussed effect of AED in the intercritical EA (Jawad et al., 1986; Milligan et al., 1982; Pro et al., 2009; Rocamora et al., 2006). In fact, the percentage of medicated epileptic seizures patients by the time of late EEG was greater than in early EEG (92.3%. vs. 38.5%). On the other hand, the likelihood of finding EA in the EEG seems to decrease over time after a paroxysmal event (Sundaram et al., 1990). The lack of a significant difference in the incidence of EA in the EEG of patients with the final diagnosis of seizure and TIA is likely to be due to small patient numbers in each subgroup.

The time evolution pattern of FSWA was significantly different between the two final diagnostic groups (seizures and TIA), as patients with seizures more often had FSWA persisting in the late EEG. The high percentage of epileptic seizure patients with early FSWA and the persistence of FSWA in the late EEG in these patients, may represent a neurophysiologic marker of the existence of an enduring predisposition to generate epileptic seizures (Fisher et al., 2005, 2014). In fact, FSWA has been described in patients with epilepsy as a good marker of the epileptogenic network and the ictal onset zone (Brigo, 2011; Di Gennaro et al., 2003; Tao et al., 2011; Vanrumste et al., 2005). In contrast, patients with definitive TIA had a different FSWA time evolution pattern: either they never had FSWA in the early EEG or the FSWA was no longer present in the late EEG, in accordance with what was described in transitory cerebral ischemia due to carotid compression (Meyer et al., 1965).

This work has some strengths, such as: 1) it compares EEG differences between patients who initially had transient neurological symptoms and a not yet established neurological diagnosis, reflecting the clinical practice diagnostic question - is the EEG useful when the diagnose is unknown?; 2) EEG readers were blind to the final diagnosis, which was established only after the EEG report; 3) no patients were lost for clinical follow-up and only a

few (7.7%) for the EEG follow-up; and 4) the high final diagnosis interobserver agreement gives robustness to the results. Nevertheless, this study also has some limitations, in particular: 1) it was hospital-based limiting generalization to other clinical settings; 2) A time-based TIA definition was used, so these results may not apply to tissue-based defined TIA (Albers et al., 2002; Easton et al., 2009); 3) Only two EEG abnormalities were variables of interest in this study but others could be considered; 4) the sample size was modest, which limits the statistical power for some comparisons.

5. Conclusions

In the early EEG, the majority (58.3%) of patients with a final diagnosis of an epileptic seizure did not have EA. FSWA in the early EEG occurred whether the patient suffered a seizure or TIA (and was more often present than EA following a seizure), but in the EEG performed 1 month after the clinical episode was more likely to indicate that the initial event was a seizure.

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Conflict of interest

The authors have completed the Unified Competing Interests form and declare that: Dr. Bentes received the 2012 Research Grant in Cerebrovascular Diseases (Scientific Promoter: Sociedade Portuguesa do AVC - Sponsor: Tecnifar). Dr. Ferro reports personal fees from Boehringer Ingelheim, and personal fees from Daiichi Sankyo, outside the submitted work. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cnp.2017.10.001.

References

A.C. Who for the N.I. of N.D. and B., 1975. A classification and outline of cerebrovascular diseases II. Stroke 6, 564–616. https://doi.org/10.1161/01.STR.6.5.564.

Albers, G.W., Caplan, L.R., Easton, J.D., Fayad, P.B., Mohr, J.P., Saver, J.L., Sherman, D. G., 2002. Transient ischemic attack – proposal for a new definition. N. Engl. J. Med. 347, 1713–1716. https://doi.org/10.1056/NEJMsb020987.

American Clinical Neurophysiology Society, 2006a. Guideline 5: guidelines for standard electrode position nomenclature. Clin. Neurophysiol. 6, 1–3 https://doi.org/10.1080/10865085X.2006.11079580.

American Clinical Neurophysiology Society. Guideline 4: Standards of Practice in Electroencephalography, 2006.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR. American Psychiatric Publishing Inc, Washington D.C..

Beniczky, S.A., Fogarasi, A., Neufeld, M., Andersen, N.B., Wolf, P., van Emde Boas, W., Beniczky, S., 2012. Seizure semiology inferred from clinical descriptions and from video recordings. How accurate are they? Epilepsy Behav. 24, 213–215. https://doi.org/10.1016/j.yebeh.2012.03.036.

Brigo, F., 2011. Intermittent rhythmic delta activity patterns. Epilepsy Behav. 20, 254–256. https://doi.org/10.1016/j.yebeh.2010.11.009.

Calanchini, P.R., Swanson, P.D., Gotshall, R.A., Haerer, A.F., Poskanzer, D.C., Price, T. R., Conneally, P.M., Dyken, M.L., Futty, D.E., 1977. Cooperative study of hospital frequency and character of transient ischemic attacks IV. The reliability of diagnosis. JAMA 238, 2029–2033. https://doi.org/10.1001/jama.1977.03280200041015.

Caplan, L., 1985. Transient global amnesia. In: Vinken, P.J., Bruyn, G.W., Klawans, H. L. (Eds.), Handbook of Clinical Neurology. Elsevier, Amsterdam, pp. 205–218.

Carreño, M., 2008. Recognition of nonepileptic events. Semin. Neurol. 28, 297–304. https://doi.org/10.1055/s-2008-1079334.

Castle, J., Mlynash, M., Lee, K., Caulfield, A.F., Wolford, C., Kemp, S., Hamilton, S., Albers, G.W., Olivot, J.-M., 2010. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. Stroke 41, 1367–1370. https://doi.org/10.1161/STROKEAHA.109.577650.

Cocito, L., Loeb, C., 1989. Focal epilepsy as a possible sign of transient subclinical ischemia. Eur. Neurol. 29, 339–344.

Correia, M., Fonseca, A.C., Canhao, P., 2015. Short-term outcome of patients with possible transient ischemic attacks: a prospective study. BMC Neurol. 15, 78. https://doi.org/10.1186/s12883-015-0333-1.

D'Ambrosio, R., Miller, J.W., 2010. What is an epileptic seizure? Unifying definitions in clinical practice and animal research to develop novel treatments Epilepsy Curr. 10, 61–66. https://doi.org/10.1111/j.1535-7511.2010.01358.x.

De Reuck, J., Van Maele, G., 2009. Transient ischemic attacks and inhibitory seizures in elderly patients. Eur. Neurol. 62, 344–348. https://doi.org/10.1159/000240647.

Deacon, C., Wiebe, S., Blume, W.T., McLachlan, R.S., Young, G.B., Matijevic, S., 2003. Seizure identification by clinical description in temporal lobe epilepsy: how accurate are we? Neurology 61, 1686–1689. https://doi.org/10.1212/01.WNL.0000090566.40544.04.

Di Gennaro, G., Quarato, P.P., Onorati, P., Colazza, G.B., Mari, F., Grammaldo, L.G., Ciccarelli, O., Meldolesi, N.G., Sebastiano, F., Manfredi, M., Esposito, V., 2003. Localizing significance of temporal intermittent rhythmic delta activity (TIRDA) in drug-resistant focal epilepsy. Clin. Neurophysiol. 114, 70–78. https://doi.org/10.1016/S1388-2457(02)00332-2.

Dolmans, L.S., Rutten, F.H., Bartelink, E.I., Seppenwoolde, M.-L., van Delft, G., Kappelle, S., Hoes, L.J., A.W., 2015. Serum biomarkers for the early diagnosis of TIA: the MIND-TIA study protocol. BMC Neurol. 15, 119. https://doi.org/10.1186/s12883-015-0388-z.

Easton, J.D., Saver, J.L., Albers, G.W., Alberts, M.J., Chaturvedi, S., Feldmann, E., Hatsukami, T.S., Higashida, R.T., Johnston, S.C., Kidwell, C.S., Lutsep, H.L., Miller, E., Sacco, R.L., 2009. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the american heart association/american stroke association stroke council; council on cardiovascular surgery and anesthesia; council on cardio. Stroke 40, 2276–2293. https://doi.org/10.1161/STROKEAHA.108.192218.

Ferracci, F., Moretto, G., Gentile, M., Kuo, P., Carnevale, A., 2000. Can seizures be the only manifestation of transient ischemic attacks? a report of four cases. Neurol. Sci. 21, 303–306. https://doi.org/10.1007/s100720070067.

Ferro, J.M., Falcao, I., Rodrigues, G., Canhao, P., Melo, T.P., Oliveira, V., Pinto, A.N., Crespo, M., Salgado, A.V., 1996. Diagnosis of transient ischemic attack by the nonneurologist: a validation study. Stroke 27, 2225–2229. https://doi.org/10.1161/01.STR.27.12.2225.

Fisher, C.M., 1962. Concerning recurrent transient cerebral ischemic attacks. Can. Med. Assoc. J. 86, 1091–1099.

Fisher, C.M., 1978. Transient paralytic attacks of obscure nature: the question of non-convulsive seizure paralysis. Can. J. Neurol. Sci. 5, 267–273.

Fisher, R.S., Boas, W., van, E., Blume, W., Elger, C., Genton, P., Lee, P., Engel, J., 2005. Epileptic seizures and epilepsy: definitions proposed by the international league against epilepsy (ilae) and the international bureau for epilepsy (IBE). Epilepsia 46, 470–472. https://doi.org/10.1111/j.0013-9580.2005.66104.x.

Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel, J., Forsgren, L., French, J.A., Glynn, M., Hesdorffer, D.C., Lee, B.I., Mathern, G.W., Moshé, S.L., Perucca, E., Scheffer, I.E., Tomson, T., Watanabe, M., Wiebe, S., 2014. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55, 475–482. https://doi.org/10.1111/epi.12550.

Flink, R., Pedersen, B., Guekht, A.B., Malmgren, K., Michelucci, R., Neville, B., Pinto, F., Stephani, U., Ozkara, C., 2002. Commission of european affairs of the international league against Epilepsy: subcommission on european guidelines, guidelines for the use of eeg methodology in the diagnosis of epilepsy. International league against epilepsy: commission report. Commission on european affairs: subcommission on european guidelines. Acta Neurol. Scand. 106, 1–7.

Fonseca, A.C., Canhão, P., 2011. Diagnostic difficulties in the classification of transient neurological attacks. Eur. J. Neurol. 18, 644–648. https://doi.org/10.1111/j.1468-1331.2010.03241.x.

Gregory, R.P., Oates, T., Merry, R.T.G., 1993. Electroencephalogram epileptiform abnormalities in candidates for aircrew training. Electroencephalogr. Clin. Neurophysiol. 86, 75–77. https://doi.org/10.1016/0013-4694(93)90069-8.

Headache Classification Subcommittee of the International Headache Society, 2004. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 24 Suppl 1, pp. 9–160.

Hirsch, L.J., LaRoche, S.M., Gaspard, N., Gerard, E., Svoronos, A., Herman, S.T., Mani, R., Arif, H., Jette, N., Minazad, Y., Kerrigan, J.F., Vespa, P., Hantus, S., Claassen, J., Young, G.B., So, E., Kaplan, P.W., Nuwer, M.R., Fountain, N.B., Drislane, F.W., 2013. American clinical neurophysiology society's standardized critical care EEG terminology: 2012 version. J. Clin. Neurophysiol. 30, 1–27. https://doi.org/10.1097/WNP.0b013e3182784729.

Hodges, J.R., Warlow, C.P., 1990. Syndromes of transient amnesia: towards a classification. A study of 153 cases. J. Neurol. Neurosurg., Psychiat. 53, 834–843. https://doi.org/10.1136/jnnp.53.10.834.

Jawad, S., Oxley, J., Yuen, W., Richens, A., 1986. The effect of lamotrigine, a novel anticonvulsant, on interictal spikes in patients with epilepsy. Br. J. Clin. Pharmacol. 22, 191–193. https://doi.org/10.1111/j.1365-2125.1986.tb05249.x.

Jin, B., Wu, H., Xu, J., Yan, J., Ding, Y., Wang, Z.I., Guo, Y., Wang, Z., Shen, C., Chen, Z., Ding, M., Wang, S., 2014. Analyzing reliability of seizure diagnosis based on semiology. Epilepsy Behav. 41C, 197–202. https://doi.org/10.1016/j.yebeh.2014.09.057.

Kaplan, P.W., 1993. Focal seizures resembling transient ischemic attacks due to subclinical ischemia. Cerebrovasc. Dis. 3, 241–243. https://doi.org/10.1159/000108708.

Kidwell, C.S., Warach, S., 2003. Acute ischemic cerebrovascular syndrome: diagnostic criteria. Stroke 34, 2995–2998. https://doi.org/10.1161/01.STR.0000098902.69855.A9.

Kraaijeveld, C.L., van Gijn, J., Schouten, H.J., Staal, A., 1984. Interobserver agreement for the diagnosis of transient ischemic attacks. Stroke 15, 723–725. https://doi.org/10.1161/01.STR.15.4.723.

Larner, A., 2011. A Dictionary of Neurological Signs. Springer New York, New York, NY. 10.1007/978-1-4419-7095-4.

Lee, H., Lerner, A., 1990. Transient inhibitory seizures mimicking crescendo TIAs. Neurology 40, 165–166.

Martins da Silva, A., Bentes, C., Atalaia, A., Mendes-Ribeiro, J.A., 2011. Recomendações para utilização do electroencefalograma (EEG) em Epilepsia: Relatório à Liga Portuguesa Contra a Epilepsia.

Meyer, J.S., Gotoh, F., Favale, E., 1965. Effects of carotid compression on cerebral metabolism and electroencephalogram. Electroencephalogr. Clin. Neurophysiol. 19, 362–376. doi: 10.1016/0013-4694(65)90161-6.

Milligan, N., Dhillon, S., Oxley, J., Richens, A., 1982. Absorption of diazepam from the rectum and its effect on interictal spikes in the EEG. Epilepsia 23, 323–331.

Muraga, K., 2016. Limb-shaking TIA: cortical myoclonus associated with ICA stenosis. Neurology 86, 307–310. https://doi.org/10.1212/WNL.0000000000002293.

National Institute for Health and Care Excelence, (NICE), 2012. Epilepsies : diagnosis and management. Clinical guideline 137.

Noachtar, S., Binnie, C., Ebersole, J., Mauguière, F., Sakamoto, A., Westmoreland, B., 1999. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. Electroencephalogr. Clin. Neurophysiol. Suppl. 52, 21–41. https://doi.org/10.1055/s-2003-812583.

Nuwer, M., Comi, G., Emerson, R., Fuglsang-Frederiksen, A., Guérit, J., Hinrichs, H., Ikeda, A., Luccas, F., Rappelsburger, P., 1998. IFCN standards for digital recording of clinical EEG. International Federation of Clinical Neurophysiology. Electroencephalogr. Clin. Neurophysiol. 106, 259–261.

Prabhakaran, S., Silver, A.J., Warrior, L., McClenathan, B., Lee, V.H., 2008. Misdiagnosis of transient ischemic attacks in the emergency room. Cerebrovasc. Dis. 26, 630–635. https://doi.org/10.1159/000166839.

Primavera, A., Giberti, L., Cocito, L., 1993. Focal inhibitory seizures as the presenting sign of ischemic cerebrovascular disease. Ital. J. Neurol. Sci. 14, 381–384.

Pro, S., Vicenzini, E., Pulitano, P., Li Voti, P., Zarabla, A., Randi, F., Mecarelli, O., 2009. Effects of levetiracetam on generalized discharges monitored with ambulatory EEG in epileptic patients. Seizure 18, 133–138. https://doi.org/10.1016/j.seizure.2008.08.004.

Robin, J.J., Tolan, G.D., Arnold, J.W., 1978. Ten year experience with abnormal EEGs in asymptomatic adult males. Aviat. Sp. Environ. Med. 49, 732–736.

Rocamora, R., Wagner, K., Schulze-Bonhage, A., 2006. Levetiracetam reduces frequency and duration of epileptic activity in patients with refractory primary generalized epilepsy. Seizure 15, 428–433. https://doi.org/10.1016/j.seizure.2006.05.012.

Salinsky, M., Kanter, R., Dasheiff, R.M., 1987. Effectiveness of multiple eegs in supporting the diagnosis of epilepsy: an operational curve. Epilepsia 28, 331–334. https://doi.org/10.1111/j.1528-1157.1987.tb03652.x.

Samson-Dollfus, D., Vernier, L., Senant, J., 1991. Electroencephalography and normal aging. Neurophysiol. Clin. 21, 345–355.

Scottish Intercollegiate Guidelines Network, (SIGN), 2015. Diagnosis and management of epilepsy in adults. A national clinical guideline (SIGN 143).

Sundaram, M., Hogan, T., Hiscock, M., Pillay, N., 1990. Factors affecting interictal spike discharges in adults with epilepsy. Electroencephalogr. Clin. Neurophysiol. 75, 358–360. https://doi.org/10.1016/0013-4694(90)90114-Y.

Tao, J.X., Chen, X.J., Baldwin, M., Yung, I., Rose, S., Frim, D., Hawes-Ebersole, S., Ebersole, J.S., 2011. Interictal regional delta slowing is an EEG marker of epileptic network in temporal lobe epilepsy. Epilepsia 52, 467–476. https://doi.org/10.1111/j.1528-1167.2010.02918.x.

Vanrumste, B., Jones, R.D., Bones, P.J., Carroll, G.J., 2005. Slow-wave activity arising from the same area as epileptiform activity in the EEG of paediatric patients with focal epilepsy. Clin. Neurophysiol. 116, 9–17. https://doi.org/10.1016/j.clinph.2004.07.032.

York, G.K., Steinberg, D.A., 2011. Hughlings Jackson's neurological ideas. Brain 134, 3106–3113. https://doi.org/10.1093/brain/awr219.

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Post-stroke epilepsy frequency/incidence: a protocol for a systematic review and meta-analysis of observational studies

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Review question(s)
To better estimate the incidence and risk of epilepsy after stroke.

To explore which conditions are associated with a higher risk of having epilepsy after stroke.

Searches
Electronic database identification of reports will be conducted in MEDLINE, EMBASE, Web of Science and PsycINFO.

Grey literature will be searched via appropriate databases (i.e.: OpenGrey). The last search will be done on 27 February 2015.

No language or time restrictions will be applied.

Non-English reports will be translated.

Whenever needed author will be contacted for further access to data.

Furthermore, potential eligible studies/selected studies' reference lists will be crosschecked for additional studies and cited reference research will be done using studies' titles and authors.

The developed search strategy for all database combines the terms (Cerebrovascular disorder OR Stroke OR Brain Ischemia OR Brain Infarction OR Intracranial Embolism and Thrombosis OR Intracranial Hemorrhage OR Cerebral Hemorrhage OR Subarachnoid Hemorrhage OR Cerebral Infarction OR Cerebellar Infarction OR Cerebellar Heamorrage OR Brain Stem Infarction OR Brain Stem Hemorrage) with (Partial Epilepsy OR Generalized Epilepsy OR Post-Traumatic Epilepsy OR Reflex Epilepsy OR Seizure OR Status Epilepticus). An sensible filter will be adapted to avoid retrieval of non-observational studies[17]. The search strategy will be restricted to humans as participants. All terms will be searched as free-text and controlled vocabulary (i.e.: Medical Subjects Headings (MeSH), EMTREE)

Types of study to be included
Published observational studies reporting original data on the frequency of epileptic phenomena after stroke in adult (>=18 years old).

To be included, studies have to clearly mention that this data was a pre-specified outcome of the study.

All observational study designs will be accepted with the exception of case series of less than 10 patients. This minimum number was arbitrarily chosen to exclude single case reports and small series, therefore decreasing the risk of selection bias. Patients diagnosed with silent central nervous system infarcts and silent cerebral hemorrhage will be excluded due to the low specificity to determine a time sequent between the cause and the effect. No study will be dismissed a priori due to poor quality.

Condition or domain being studied

On 2005 the International League Against Epilepsy and the International Bureau for Epilepsy consensually defined epilepsy as a brain disorder characterized by a predisposition to have epileptic seizures – paroxysms of neurologic clinical symptoms and/or signs of abnormally excessive or synchronized brain neuronal discharge - and by the biological, social, cognitive e psychological consequences of having it. Although two unprovoked seizures had been indispensable for the formal diagnosis of epilepsy to be done, it is currently accepted that when the risk of having a second event after the first event is the same or even higher of having a third event after a second event, an epilepsy diagnosis can be made. Etiologic conditions such as stroke can place a patient in such conditions.

Stroke is characterized by an acute focal central nervous tissue injury – infarction, due to a vascular insult, such as embolism, thrombosis or haemorrhage - causing a neurological clinical deficit. Although its incidence is decreasing, absolute figures show that stroke is an increasingly common condition - in part due to population aging and the positive linear relation between age and stroke incidence.

It is also known that there is an increased risk of epilepsy after stroke – also called post-stroke epilepsy – and that stroke is of paramount importance as an aetiology factor for epilepsy in the elderly population. Given the above, incidence and prevalence of post-stroke epilepsy is expected to rise.

Nonetheless little is known about the incidence of post-stroke epilepsy and which clinical characteristics pose a patient at a higher risk of having post-stroke epilepsy.

Participants/ population

Published observational studies reporting original data on the frequency of epileptic phenomena after stroke in adult (>=18 years old).

To be included, studies have to clearly mention that this data was a pre-specified outcome of the study.

All observational study designs will be accepted with the exception of case series of fewer than 10 patients. This minimum number was arbitrarily chosen to exclude single case reports and small series, therefore decreasing the risk of selection bias. Patients diagnosed with silent central nervous system infarcts and silent cerebral hemorrhage will be excluded due to the low specificity to determine a time sequent between the cause and the effect. No study will be dismissed a priori due to poor quality.

Intervention(s), exposure(s)

Published observational studies reporting original data on the frequency of epileptic phenomena after stroke in adult (>=18 years old).

To be included, studies have to clearly mention that this data was a pre-specified outcome of the study.

All observational study designs will be accepted with the exception of case series of fewer than 10 patients. This minimum number was arbitrarily chosen to exclude single case reports and small series, therefore decreasing the risk of selection bias. Patients diagnosed with silent central nervous system infarcts and silent cerebral hemorrhage will be excluded due to the low specificity to determine a time sequent between the cause and the effect. No study will be dismissed a priori due to poor quality.

Comparator(s)/ control

Not applicable.

Outcome(s)

Primary outcomes

Our primary outcome is the frequency of post-stroke epilepsy amongst stroke patients. The frequency of post-stroke epilepsy will be estimated for different subgroup of patients according to age (

assessment tool (A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT- NRSI)). Studies having a star rating of more than 60% for the respective study design will be considered of good quality, as done by other authors. The quality of reporting will be independently analyzed by two authors. Disagreements will be solved by consensus or by a third independent party (JC). Since the efficacy of blind quality assessment is not proven, titles, author and results will not be blacked out before appraisal.

Strategy for data synthesis

We will use a validated statistical software for conducting the analysis and to derive forest plots showing the results of individual studies and pooled analysis. Random-effects meta-analysis weighted by the inverse-variance method will be performed to estimate pooled incidence per 100,000 individuals/frequency and 95% confidence intervals (CI), and RR/OR and 95% CI. Heterogeneity will be assessed with the I-squared test and the Cochran Q test. We will use a random-effects model as substantial heterogeneity between study results is expected. The effect measurement estimate chosen will be RR/OR because relative estimates are more similar across studies with different designs, populations and lengths of follow-up than absolute effects. Raw data will be first converted to RR/OR through classic methods or through the Peto method if one arm had a zero-count cell. When raw data or RR/OR are not available we will took the hazard ratio or risk ratio for analysis. A p-value of 0.05 will be considered significant at a 95% confidence level.

Analysis of subgroups or subsets

Sensitivity analysis will be conducted for different definitions of epilepsy, study type design and overall study quality.

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Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
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Frequency of post-stroke electroencephalographic epileptiform activity – a systematic review and meta-analysis of observational studies

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Abstract

Introduction: Cerebrovascular diseases are the most frequent risk factor for epilepsy in the elderly, and epileptic phenomenon following stroke is known to worsen the prognosis. Although electroencephalography is the gold standard epilepsy biomarker, it is rarely used in post-stroke studies, and the frequency of post-stroke epileptiform activity is still uncertain.

Patients and methods: We analysed studies indexed to MEDLINE, Embase, Web of Science, PsycINFO and OpenGrey (up to March 2015), reporting post-stroke electroencephalographic epileptiform activity frequency in adults. Epileptiform activity was classified as ictal (electrographic seizures) and interictal (non-periodic spikes and sharp waves). Data selection, extraction and appraisal were done in duplicate. Random-effects meta-analysis was used to pool frequencies.

Results: The pooled frequency of post-stroke ictal and interictal epileptiform activity was 7% (95% CI 3%–12%) and 8% (95% CI 4%–13%), respectively. The use of continuous electroencephalogram was not associated with an increased frequency of electrographic seizures ($p = 0.05$), nor did the management setting (Intensive Care Unit versus non-Intensive Care Unit, $p = 0.31$). However, studies with continuous electroencephalogram showed a higher frequency of interictal epileptiform activity ($p = 0.01$).

Discussion: This study provides the best available estimates of the frequency of post-stroke electroencephalographic epileptiform activity. Due to detection bias, it was not possible to correlate clinical and electrographic seizures.

Conclusion: The frequency of ictal and interictal epileptiform activity in the electroencephalogram was comparable with previous frequency analyses of clinical seizures. The frequency of ictal epileptiform activity did not change with continuous record or clinical setting, while the frequency of interictal epileptiform activity increased with continuous record.

Keywords

Epileptic seizures, stroke, electroencephalogram, systematic review, meta-analysis

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Introduction

Cerebrovascular diseases are the most frequent risk factor for epilepsy,[1] accounting for more than half of all cases in elderly patients.[2] On the other hand, epileptic seizures following stroke[3,4] and electrographic seizures and interictal epileptiform discharges in critically ill patients are known to worsen the outcome.[5–7]

The current International League Against Epilepsy (ILAE) definition of epilepsy[8] allows for the diagnosis of epilepsy after a single unprovoked seizure, provided that there is at least a 60% probability of recurrence, as it is the case of the first unprovoked seizure after the acute stroke phase.[3] This sensitivity-maximising definition, and the fact that acute symptomatic seizures are described as risk factors for unprovoked seizures,[9] prompts discussion for the role of electroencephalogram (EEG) after stroke – as this technique can contribute to early and accurate detection of ictal and interictal epileptiform activity.

The frequency of seizures and interictal epileptiform activity after stroke is uncertain.[10] This is the case because EEG is seldom used in studies investigating the frequency of post-stroke seizures, although being the gold standard for the identification of these phenomena,[11] and as little as 10% of all seizures are recognised without EEG in critically ill patients.[12]

As so, we set out to estimate the frequency of post-stroke electroencephalographic epileptiform activity using meta-analytical techniques.

Patients and methods

Protocol and registration

The protocol followed the PRISMA-P guidelines and was registered at Prospero (CRD42015029362). We followed the MOOSE and PRISMA guidelines[13]. Statistical data reporting followed the SAMPL guidelines.

Eligibility criteria

We included published and unpublished (i.e. conference proceedings) observational studies reporting original data on the frequency of electroencephalographic epileptiform activity after stroke in adults (≥18 year-old). All observational study designs were accepted with the exception of case series with less than 10 participants to decrease the risk of selection bias. This threshold was established arbitrarily and excludes single case-reports and small case series. Studies reporting on patients diagnosed with silent cerebral infarcts and haemorrhages were excluded due to the low specificity to determine a time sequence between the cause and the effect. No study was dismissed a priori due to poor quality, language or length of follow-up. Epileptiform activity in the EEG was classified as ictal activity (electrographic seizures[14]) and interictal activity (non-periodic spikes and sharp waves).[15] Stroke was defined as an episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 h or until death.[16] For data extraction and analysis we followed the above-mentioned definitions.

Information sources

The electronic search was conducted in MEDLINE, Embase, Web of Science and PsycINFO. Grey literature was searched via OpenGrey. No language, date/time, document type or publication type restriction was applied. The last search was done on 22 March 2015. Search results were de-duplicated in EndNote X7. Non-English reports were translated. Whenever needed, authors were contacted for further data. The reference lists of included studies were crosschecked for additional studies.

Search

The search strategies developed combine the terms (Cerebrovascular disorder OR Stroke OR Brain Ischemia OR Brain Infarction OR Intracranial Embolism and Thrombosis OR Intracranial Haemorrhage OR Cerebral Haemorrhage OR Subarachnoid Haemorrhage (SAH) OR Cerebral Infarction OR Cerebellar Infarction OR Cerebellar Haemorrhage OR Brain Stem Infarction OR Brain Stem Haemorrhage) with (Partial Epilepsy OR Generalized Epilepsy OR Post-Traumatic Epilepsy OR Reflex Epilepsy OR Seizure OR Status Epilepticus). A filter was adapted to avoid retrieval of non-observational studies. The search strategy was restricted to humans as participants. All terms were searched as free-text and controlled vocabulary. The search strategies can be found in the Supplemental methods.

Study selection

Reports retrieved through electronic identification were screened by title and abstract. The full-text of potentially eligible studies was screened for appropriateness for inclusion. Three independent screeners (CB, DS and RP) conducted this process. Disagreements were solved by consensus, or by a fourth party (FBR).

Data collection process

A pilot extraction form was tested with five studies by two independent reviewers (CB and FBR). Two independent parties (AF, DS, GSD, HN, RM or RP)

extracted data from included studies to a predetermined and piloted electronic form using the online-based software Covidence (https://www.covidence.org/). Disagreements were solved by an independent party (CB or FBR).

Risk of bias in individual studies

The risk of bias of individual studies was evaluated in accordance with the Newcastle–Ottawa Quality Assessment Scale.[17] Quality of reporting was independently analysed by two authors (AF, DS, GSD, HN, RM or RP). Disagreements were solved by a third party (CB or FBR). Studies having a star rating of more than 60% were considered of low risk of bias, as assumed by others.

Summary measures

The primary outcomes were the frequency of ictal and interictal epileptiform activity (as defined above) in stroke patients' EEGs. To calculate frequencies we adopted a conservative approach by determining the number of events divided by the number of participants in the study. This method underestimates events, since not all participants performed EEG.

Synthesis of results

We used Stata/SE 14.0 software to conduct the analysis and to derive forest plots. Random-effects meta-analysis weighted by the inverse-variance method was performed to estimate the pooled frequencies and respective 95% confidence intervals (95% CI). We used a random-effects model as substantial heterogeneity between studies results was expected. Heterogeneity was assessed with the I^2 test. The limit for statistical significance was established at 0.05.

Additional analysis

Pre-specified sensitivity analyses were conducted by excluding: studies at high and unclear risk of bias; studies without continuous EEG (cEEG); and studies in settings other than the intensive care unit (ICU). We planned to estimate the frequency of events in different subgroups of patients according to study site, year, stroke type and location. Unfortunately, we could not retrieve enough data for the latter analysis. Two post-hoc analyses were performed: the first excluding studies only reporting on SAH, to study the effect of this aetiology on the overall frequency of events; and the second solely including studies where EEG was performed in a consecutive cohort of stroke patients, to study the effect of selection bias.

Results

Study selection

The last electronic search was run from inception to 22 March, 2015. A total of 2871 references were retrieved (MEDLINE 1985, Embase 425, PsycINFO 66, Web of Science 394, Open Grey 1). Two studies were included via hand-search. After de-duplication, 2527 titles and abstracts were screened, and 2226 were excluded, as they were not relevant to our research question. We selected 301 studies for full text assessment, and 284 studies were removed due to failure to comply with inclusion criteria. A total of 17 studies where included (Figure 1, Table 1 and supplemental references).

Risk of bias within studies

Four (23.5%) studies did not meet our definition of low risk of bias. The remaining were assessed as being at a low risk of bias. Only two (11.7%) included studies attained the maximum quality score (low risk of bias in all domains).

Synthesis of results

The pooled frequency of ictal epileptiform activity (electrographic seizures) in the EEG was 7% (95% CI 3%–12%, $I^2 = 93.5\%$, 14 studies, n = 2711, Figure 2), without significant differences when considering only studies at low risk of bias (13 studies), studies exclusively enrolling participants with haemorrhagic stroke (8 studies), studies including ischemic and haemorrhagic stroke (6 studies), or after excluding studies where only SAH were captured (13 studies). Studies where EEG was performed in a consecutive cohort of stroke patients showed a smaller frequency of events (4%, 95% CI 0%–12%, $I^2 = 82.5\%$, 4 studies, n = 339). No study exclusively enrolled participants with ischemic stroke. Studies including exclusively SAH patient did not differ from the other included studies ($p = 0.77$). The use of cEEG was not associated with an increased frequency of detected electrographic seizures ($p = 0.05$), nor with the setting where the patients were tested (ICU versus non-ICU, $p = 0.31$), or the year of publication (before versus after 2007, a threshold generated by splitting the included studies into two groups according to the year of publication) ($p = 0.72$). Studies performed in the USA showed a higher frequency of electrographic seizures than studies performed outside the USA (13% (95% CI 10%–17%) versus 1% (95% CI 0%–2%); $p < 0.001$).

The pooled frequency of interictal epileptiform activity (non-periodic spikes and sharp waves) was 8% (95% CI 4%–13%, $I^2 = 86.0\%$, 7 studies, n = 1874, Figure 3). When only analysing trials at low

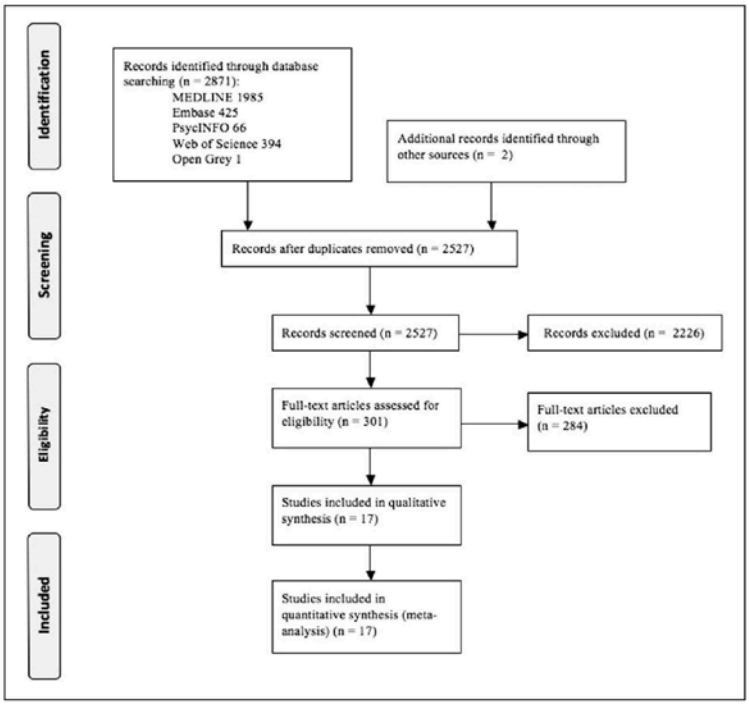

Figure 1. PRISMA flow chart.

Table 1. Characteristics of included studies.

Study (see supplementary references)	Year	Country	n	EEG type	Stroke type	Setting
Arboix 1997	1997	Spain	1220	EEG	Ischemic and haemorrhagic	Neurology department
Dhanuka 2001	2001	India	269	EEG	Ischemic and haemorrhagic	Neurology department
Velioglu 2001	2001	Turkey	1174	EEG	Ischemic and haemorrhagic	Neurology department
Vespa 2003	2003	USA	109	cEEG	Ischemic and haemorrhagic	Intensive care unit
Claassen 2004	2004	USA	209	cEEG	Ischemic and haemorrhagic	Tertiary care hospital
Carrera 2006	2006	Switzerland	100	cEEG	Ischemic and haemorrhagic	Stroke unit
Claassen 2006	2006	USA	116	cEEG	Haemorrhagic	Intensive care unit
Claassen 2007	2007	USA	102	cEEG	Haemorrhagic	Tertiary care hospital
Little 2007	2007	Italy	889	cEEG	Haemorrhagic	Tertiary care hospital
Naidech 2009	2009	USA	98	cEEG	Haemorrhagic	Tertiary care hospital
Garrett 2009	2009	USA	110	cEEG	Haemorrhagic	Tertiary care hospital
Strzelczyk 2010	2010	Germany	264	EEG	Ischemic and haemorrhagic	Neurology department
Chen 2011	2011	China	32	EEG	Ischemic and haemorrhagic	Geriatric department
Lindgren 2012	2012	Sweden	108	cEEG	Haemorrhagic	Critical care unit
Srinivasan 2013	2013	USA	138	EEG	Haemorrhagic	Tertiary care hospital
O'Connor 2014	2014	USA	69	cEEG	Haemorrhagic	Critical care unit
Swisher 2015	2015	USA	56	cEEG	Ischemic and haemorrhagic	Critical care unit

EEG: spot EEG; cEEG: continuous EEG; n: number of patient enrolled per study.

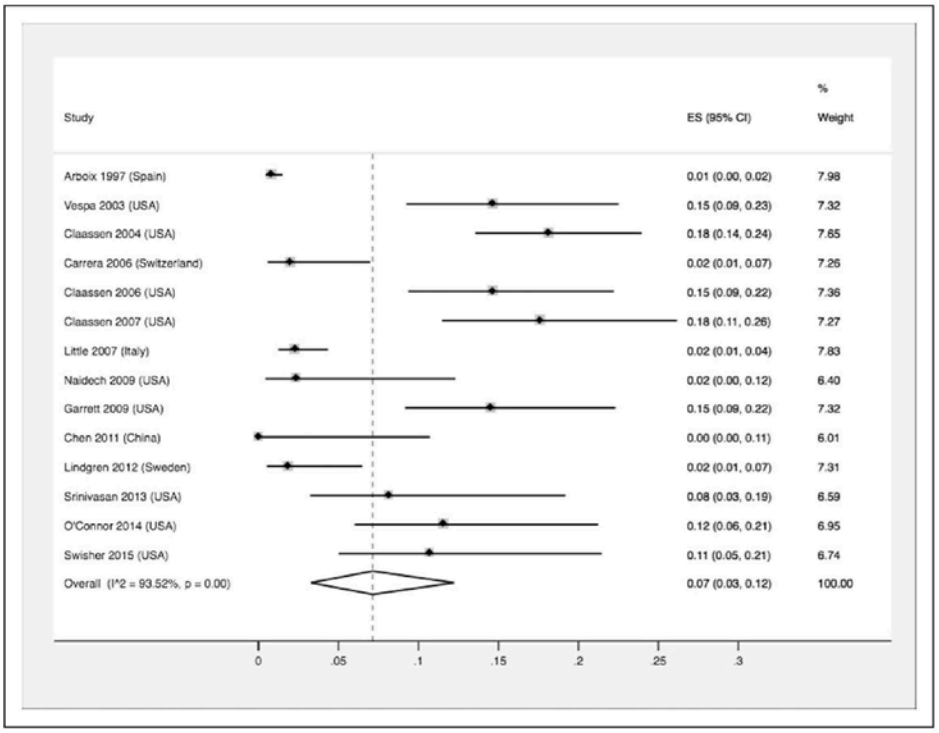

Figure 2. Pooled frequency of ictal activity (electrographic seizures). This graph shows the results of each individual study in each of the lines, and the results of the meta-analysis in the last line (lozenge). The left column presents the surname of the first author of each study, the year of publication and the country where the study was performed, with the exception of the last line, where the results of the statistical heterogeneity tests employed are presented. The two middle columns show, from the left to the right, the graphical (forest plot) and numerical representation (percentage of participants with ictal activity and a 95% confidence interval [95% CI]) of the results of each individual study and, on the last line (lozenge), of the meta-analysis. The dotted vertical line represents the central estimate of effect. Finally, the right column depicts the weight each of the studies had on the meta-analysis.

risk of bias, the estimated frequency increased to 10% (95% CI 5%–16%, $I^2 = 85.48\%$, 6 studies, n = 1810). We found no difference for studies including ischemic and haemorrhagic stroke (8%, 95% CI 3%–13%, $I^2 = 87.2\%$, 5 studies, n = 1839), though we found an increased frequency among studies exclusively enrolling haemorrhagic stroke patients (12%, 95% CI 7%–13%, $I^2 = 96.8\%$, 2 studies, n = 240). No study reported solely on patients with SAH. Studies where EEG was performed in a consecutive cohort of stroke patients showed a higher frequency of events (14%, 95% CI 9%–21%, $I^2 = 0.0\%$, 2 studies, n = 132). Studies with cEEG showed a higher frequency of interictal epileptiform activity detection (14%, 95% CI 10%–20% vs. 6%, 95% CI 3%–10%; $p = 0.01$). No study performed in ICU reported these events and no differences were found between study site ($p = 0.26$) or year of publication ($p = 0.29$).

Discussion

This systematic review and meta-analysis of observational studies shows that 7% and 8% of patients following a stroke have ictal and interictal epileptiform activity, respectively, in the EEG. To the best of our knowledge, the frequency of post-stroke electroencephalographic events in observational studies was never pooled, and such results should prompt further discussion as to whether EEG should be used more frequently after stroke as a biomarker for epileptic manifestations.

Previous systematic reviews have shown that intracerebral haemorrhages and SAH are associated with a

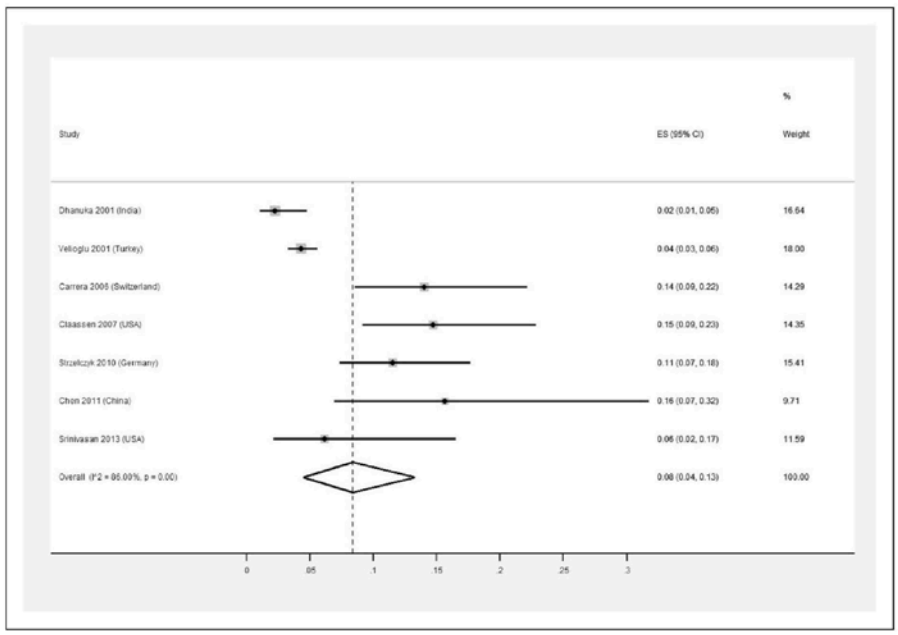

Figure 3. Pooled frequency of interictal activity (non-periodic spikes and sharp waves). This graph shows the results of each individual study in each of the lines, and the results of the meta-analysis in the last line (lozenge). The left column presents the surname of the first author of each study, the year of publication and the country where the study was performed, with the exception of the last line, where the results of the statistical heterogeneity tests employed are presented. The two middle columns show, from the left to the right, the graphical (forest plot) and numerical representation (percentage of participants with interictal activity and a 95% confidence interval [95% CI]) of the results of each individual study and, on the last line (lozenge), of the meta-analysis. The dotted vertical line represents the central estimate of effect. Finally, the right column depicts the weight each of the studies had on the meta-analysis.

significantly greater probability of epileptic seizures.[18,19] In our study, studies exclusively enrolling haemorrhagic stroke patients showed a higher frequency of interictal epileptiform activity but not of electrographic seizures. Furthermore, the frequency of events was not different in studies solely focused on SAH. Importantly, the absence of studies exclusively enrolling ischemic stroke patients may bias these results, since mixed population studies (i.e. including both ischemic and haemorrhagic stroke) are expected to set the bar for this comparison much higher, and decrease the likelihood of finding a statistically significant difference between populations. Also, the low number of studies analysing epileptiform activity in haemorrhagic stroke in general, and in SAH in specific, can also contribute to uncertainty and to unexpected results, as there is a pathophysiological rational for these stroke subtypes to be associated with more epileptiform activity.

As expected, in studies where consecutive stroke patients underwent an EEG, the frequency of ictal events was lower than our general estimate. This analysis subtracts from the selection bias introduced by retrospective studies where it is methodologically difficult to avoid a systematic error of including participants more likely to have epileptiform activity, such as those with clinical seizures or with a lower or fluctuating consciousness level. Unfortunately, our confidence in these results is low due to limited statistical power and low precision. Unexpectedly, the frequency of interictal events in these studies exceeds the general estimate, though the reason for this finding may be the lack of power, since only 2 studies were included.

In our study, cEEG did not increase the likelihood of detection of ictal epileptiform activity, which agrees with previous studies,[20] where it was stated that insufficient data exists to support the benefit of cEEG over spot EEG recordings. That being said, the detection

rate of interictal epileptiform activity with cEEG was twice as high without cEEG.

The frequency of electrographic seizures was not different in ICU and non-ICU patients. However, the scarcity of studies and the imbalances between population characteristics may bias these results.

Not unexpectedly, the year of publication did not influenced the frequency of events. On the other hand, it was interesting to note that studies conducted in the US showed a statistically significant higher frequency of ictal events. We hypothesise that this can be explained by the population characteristics, since a great majority of the North American studies were based in an intensive care setting, while this was not true for the other studies.

Finally, it is important to note that this study has several limitations. The quality assessment showed that almost 80% of the studies were at low risk of bias but only 12% had a high quality standard. Our methodological options probably underestimate electroencephalographic epileptiform activity. EEG is more likely to be requested if there is a clinical suspicion of seizures. This selection bias by indication is only avoidable in prospective studies where EEG is performed on all patients regardless of the clinical features. Studies reporting electroencephalographic epileptiform activity are not controlled with a group of participants without the pathological condition of interest, but who were subject to the same kind of clinical and diagnostic procedures. This invalidates the possibility of studying risks of events instead of frequency as we did. It would be interesting to understand how the frequency of clinical seizures relates to the frequency of electrographic ones. Unfortunately, due to diagnostic bias, since not all enrolled participants performed EEG, the available literature cannot reliably answer this question. Finally, we would like to have included the timing of the EEG in our analyses, since this variable seems to be closely related with the likelihood of detection of epileptiform events. Unfortunately this data was rarely available.

Conclusion

In conclusion, the frequency of ictal and interictal epileptiform activity in the EEG was comparable with previous frequency analyses of clinical seizures. The frequency of ictal epileptiform activity did not change with continuous record or clinical setting, while the frequency of interictal epileptiform activity increased with continuous recordings.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JMF has received personal fees from Boehringer Ingelheim. The remaining authors declare that there is no conflict of interest.

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Ethical approval

Not applicable.

Informed consent

Not applicable.

Guarantor

JC and JMF.

Contributorship

CB and JC conceived the study. FBR and JC were involved in protocol development. DS, GSD, ACF, RM, HN and ARP performed the systematic review. FBR performed the data analysis. CB, FBR and GSD wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

References

1. Hauser WA, Annegers JF and Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993; 34: 453–68.
2. Paradowski B and Zagrajek MM. Epilepsy in middle-aged and elderly people: a three-year observation. *Epileptic Disord: Int Epilepsy J Videotape* 2005; 7: 91–95.
3. Hesdorffer DC, Benn EK, Cascino GD, et al. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia* 2009; 50: 1102–1108.
4. Huang CW, Saposnik G, Fang J, et al. Influence of seizures on stroke outcomes: a large multicenter study. *Neurology* 2014; 82: 768–776.
5. Young GB, Jordan KG and Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996; 47: 83–89.
6. Oddo M, Carrera E, Claassen J, Mayer SA, et al. Continuous electroencephalography in the medical intensive care unit. *Criti Care Med* 2009; 37: 2051–2056.
7. Kamel H, Betjemann JP, Navi BB, et al. Diagnostic yield of electroencephalography in the medical and surgical intensive care unit. *Neurocrit Care* 2013; 19: 336–341.

8. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014; 55: 475–482.
9. Roivainen R, Haapaniemi E, Putaala J, et al. Young adult ischaemic stroke related acute symptomatic and late seizures: risk factors. *Eur J Neurol* 2013; 20: 1247–1255.
10. Pitkanen A, Roivainen R and Lukasiuk K. Development of epilepsy after ischaemic stroke. *Lancet Neurol* 2015.
11. Staba RJ, Stead M and Worrell GA. Electrophysiological biomarkers of epilepsy. *Neurother J Am Soc Exp NeuroTher* 2014; 11: 334–346.
12. Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 2004; 62: 1743–1748.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Int Med* 2009; 151: W65–W94.
14. Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin. Neurophys Off Publ Am Electroencephalogr Soc* 2013; 30: 1–27.
15. Noachtar S, Binnie C, Ebersole J, et al. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophys Suppl* 1999; 52: 21–41.
16. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke J Cereb Circ* 2013; 44: 2064–89.
17. GA Wells BS, D O'Connell, J Peterson, et al. Newcastle–Ottawa quality assessment scale for assessing the quality of nonrandomised studies in meta-analyses: (accessed 1 November 2014).
18. Zhang C, Wang X, Wang Y, et al. Risk factors for post-stroke seizures: a systematic review and meta-analysis. *Epilepsy Res* 2014; 108: 1806–1816.
19. Zou S, Wu X, Zhu B, et al. The pooled incidence of post-stroke seizure in 102 008 patients. *Top Stroke Rehabil* 2015; 22: 460–467.
20. Claassen J and Vespa P. Electrophysiologic monitoring in acute brain injury. *Neurocrit Care* 2014; 21(Suppl 2): S129–S147.

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ORIGINAL COMMUNICATION

Post-stroke seizures are clinically underestimated

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Abstract Cerebrovascular disease is the leading cause of epilepsy in adults, although post-stroke seizures reported frequency is variable and few studies used EEG in their identification. To describe and compare EEG and clinical epileptic manifestations frequency in patients with an anterior circulation ischaemic stroke. Prospective study of acute anterior circulation ischaemic stroke patients, consecutively admitted to a Stroke Unit over 24 months and followed-up for 1 year. All patients underwent standardized clinical and diagnostic assessment. Seizure occurrence was clinically evaluated during hospitalization and by a telephone interview at 6 months and a clinical appointment at 12 months after stroke. Video-EEG was performed in the first 72 h (1st EEG), daily after the 1st EEG for the first 7 days after the stroke, or later if neurological worsening, at discharge, and at 12 months. 151 patients were included (112 men) with a mean age of 67.4 (11.9) years. In the 1st year after stroke, 38 patients (25.2%) had an epileptic seizure. During hospitalization, 27 patients (17.9%) had epileptiform activity (interictal or ictal) in the EEG, 7 (25.9%) of them electrographic seizures. During the first week after stroke, 22 (14.6%) patients had a seizure and 4 (2.6%) non-convulsive status epilepticus criteria. Five (22.7%) acute symptomatic seizures were exclusively electrographic. At least one remote symptomatic seizure occurred in 23 (16%) patients. In the first 7 days after stroke, more than one-fifth of patients with seizures had exclusively electrographic seizures. Without a systematic neurophysiological evaluation the frequency of post-stroke seizures are clinically underestimated.

Keywords Ischaemic stroke · Symptomatic seizures · Epilepsy · EEG · Interictal epileptiform activity · Electrographic seizures

Introduction

Post-stroke seizures identification has many implications for clinical practice. One the one hand, epilepsy diagnosis can be made to a patient with at least one remote symptomatic seizure after stroke [1] since it has a recurrence probability of 71.5% [2]. One the other hand, although there is no quality evidence for the recommendation of acute symptomatic post-stroke seizures secondary prevention [3], this seems to be common in many centres in the acute stroke setting, to prevent additional metabolic burden [4].

However, the reported frequency of seizures after an ischemic stroke is variable (2–67%) [5] possibly due to different study methodologies. One limitation of this frequency analysis has been the lack (in the vast majority of studies) of an electroencephalographic record [6]. In a retrospective study of acute brain injury patients submitted to

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EEG monitoring, most seizures (92%) were electroencephalographic without apparent clinical manifestations [7]. More specifically, 9% of patients with an acute ischemic lesion had non-convulsive seizures and 7% had criteria for non-convulsive status epilepticus [7]. Thus, in the absence of an EEG record, the frequency of post-stroke seizures may be underestimated. Moreover, the frequency of electrographic seizures in patients with ischemic stroke who do not require admission to an intensive care unit and EEG monitoring is unknown, although epileptic seizures [2, 8] and ictal/interictal EEG discharges have been associated with stroke unfavourable outcome [9–11].

This paper aims to prospectively describe and compare the frequency of EEG and clinical epileptic manifestations in patients with an anterior circulation ischaemic stroke admitted to a Stroke Unit.

Methods

Prospective study of consecutive patients with an acute anterior circulation ischaemic stroke, admitted to the Stroke Unit of a Neurology Department over a period of 24 months (between October 2011 and October 2013) and followed-up for 12 months (October 2012 to October 2014). The study was approved by the Ethics Committee of Centro Hospitalar Lisboa Norte ("Comissão de Ética para a Saúde").

The following inclusion criteria were used:

1. Acute anterior circulation ischaemic stroke, established by imaging (CT scan or MRI) obtained at any time during hospitalization (reviewed by a senior neuroradiologist), with less than 7 days of clinical evolution
2. National Institutes of Health Stroke Scale (NIHSS) score [12] ≥4 upon admission to the emergency department
3. Signed informed consent by the patients or their next-of-kin.

The subsequent exclusion criteria were used:

1. Previous stroke with modified Rankin scale score (mRS) [13–15] >1 at the time of acute stroke.
2. Brain imaging study (CT scan or MRI) with one of the following: contusion; subdural/epidural hematoma; subarachnoid haemorrhage; neoplastic lesion; infectious/inflammatory lesion; hydrocephalus.
3. Previous history of head trauma with hospital admission.
4. Previous neurosurgery.
5. Previous history of epilepsy or epileptic seizures.

Standardized clinical and ancillary evaluation

All patients were attended by a neurologist at the emergency department and admitted at the Stroke Unit with continuous surveillance of their neurological status and daily observation by a stroke neurologist. During hospitalization, the patients underwent diagnostic tests allowing stroke etiological classification [16] and appropriate therapeutic approach, including blood tests, carotid and vertebral duplex scans, transcranial Doppler and ECG. All patients underwent a CT scan at the emergency department (1st CT scan) which was repeated 24 h after stroke in patients submitted to intravenous thrombolysis with alteplase (rtPA) and when clinically indicated in all patients (2nd CT scan). In selected cases, patients also performed MRI with diffusion weighted imaging, transthoracic or transesophageal echocardiography, 24 h Holter or cerebral angiography. NIHSS score at hospital admission, after rtPA perfusion, daily and at discharge was registered prospectively (CB and HM). During hospitalization, the following clinical, laboratory and treatment variables were daily recorded: fever/infection (respiratory, urinary, other)/organ failure (kidney, liver, heart)/withdrawal syndrome/hydroelectrolytic imbalance/hypoxemia/seizure occurrence/other medical or neurological complication/pharmacological therapy (CB and HM).

After discharge the patient maintained standard clinical follow-up at the cerebrovascular outpatient clinic. A neurologist with expertise in epilepsy (CB) performed a telephone interview 6 months after stroke accessing seizure occurrence by a free interview followed by a brief phone screening tool for identifying patients with epilepsy [17]. A scheduled appointment 12 months after stroke was also conducted (CB), recording the following clinical variables: NIHSS and mRS scores, occurrence of seizures and its type; other stroke or medical complications; final etiological classification of stroke [16] and on-going therapy.

Neurophysiological evaluation

All patients underwent a neurophysiological evaluation protocol that included a 64 channels video-EEG with a maximum duration of 60 min in different time frames after stroke:

1. As early as possible, in the first 72 h after admission (1st EEG).
2. Daily, after the 1st EEG, for the first 7 days after stroke (except on weekend).
3. If neurological worsening unexplained by medical complications and with indication for repeating the imaging exam.
   EEGs referred in (2) and (3), were called serial EEG study during hospitalization.
4. At time of clinical discharge (discharge EEG).

5. At 12 months after stroke (12 M EEG).

The EEG record followed national and international recommendations [18–22]. Video-EEG was performed using a Nihon-Kohden device (Neurofax EEG-1200) with a sampling frequency of 1000 Hz. We used international 10/10 electrodes placement system and recorded at least 64 EEG channels. The total recording period was at least 35 min of wakefulness, including activation tests. Sleep was recorded whenever possible at the end of the exam. All records were performed by neurophysiology technicians with expertise in video-EEG and EEG records in acute brain lesion patients. Further technical specifications and EEG protocol can be read in supplementary file 1.

Imaging interpretation

All imaging exams performed during the study period were reviewed by two seniors neuroradiologists (CC and CM), blinded for clinical and electroencephalographic findings and trained for ASPECTS classification [23]. Doubts were discussed by consensus.

In patients with an infarct limited to the middle cerebral artery (MCA) territory in the imaging study (considering 1st CT scan, 2nd CT scan or MRI), the infarct size was quantified by ASPECTS [24] in 1st and 2nd CT scan. Insula and M1 to M6 ASPECTS territories were considered "cortical territories of ASPECTS". Furthermore, any type of haemorrhage transformation [25], cortical or subcortical infarct location, presence of cortical areas with normal attenuation coefficient (islands of preserved cortex) within the infarct [26–28] were evaluated in 2nd CT.

Operational definitions

1. Epileptic seizures and status epilepticus (only the first event was considered), were defined as:

    1.1. *Epileptic seizure;* Clinical [1] and/or electrographic seizure [29, 30]
    1.2. *Acute symptomatic seizure;* Seizure occurring within the first 7 days of a stroke [31]. In these patients, cutoff values for metabolic disorders and febrile symptomatic seizures were not overreached and alcohol/drug withdrawal or intoxication [31] were excluded
    1.3. *Remote symptomatic seizure;* Seizures occurring after 7 days of a stroke in the absence of precipitating factors [32]
    1.4. *Epilepsy;* Occurrence of one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years [1]. The occurrence of at least one remote symptomatic seizure or unprovoked seizure after stroke meets these criteria [2]
    1.5. *Status epilepticus;* ILAE classification [33] and Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus (NCSE) [30, 34]

2. Electroencephalographic abnormalities:

    2.1. Occurrence in the 1st EEG of:

    – *Interictal epileptiforme activity (IEA)* [35]; EEG transients distinguishable from background activity with a characteristic spiky morphology, namely sharp waves (duration of 70–200 ms) and spikes (duration of 20–70 ms).
    – *Periodic discharges (PD)* [29]; Repetition of a waveform (with no more than three phases or any waveform lasting ≤0.5 s regardless of number of phases) with relatively uniform morphology and duration with a quantifiable inter-discharge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals.
    – *Electrographic (EEG) seizures* [29, 30]; Generalized spike-wave discharges at 3/s or faster or clearly evolving discharges of any type that reach a frequency >4/s, whether focal or generalized. Evolving was defined as at least two unequivocal, sequential changes in frequency, morphology or location lasting for at least three cycles each. Evolution in frequency was defined as at least two consecutive changes in the same direction by at least 0.5/s. Evolution in morphology was defined as at least two consecutive changes to a novel morphology. Evolution in location was defined as sequentially spreading into or sequentially out of at least two different standard 10–20 electrode locations.

    2.2. Any EEG during hospitalization (1st EEG or serial EEG study during hospitalization) with IEA and/or EEG seizures

Statistical analysis

A descriptive analysis was used for nominal qualitative and quantitative (discrete and continuous) variables. Nominal variables are expressed in frequency, the discrete variables as medians and interquartile ranges (IQR) and continuous variables as means and standard deviations (SD).

Statistical analysis was done using SPSS program version 24 for Mac.

Results

151 patients (112 men and 39 women) with an acute anterior circulation ischaemic stroke and a mean age of 67.4 (SD 11.9) years were included. Study flowchart was previously described [36].

Demographic, clinical and imaging characteristics of these patients are displayed in Table 1.

All patients performed at least one EEG during hospitalization. The 1st EEG was performed in a median time of 1 day (IQR 1). The median number of tests performed per patient was 5 (IQR 3).

Table 1 Demographic, clinical and imaging characteristics of anterior circulation stroke patients

Demographic and clinical characteristics ($n = 151$)	
Number of male/female patients (%)	112/39 (74.2%/25.8%)
Mean age (SD)	67.4 (11.9)
Median NIHSS at admission (IQR)	12 (10)
Number of patients treated with intravenous alteplase (%)	101 (67.3%)
Stroke aetiology	
Cardioembolism	77 (51.0%)
Large-artery atherosclerosis	37 (24.5%)
Small-vessel occlusion	4 (2.6%)
Undetermined aetiology	29 (19.2%)
Other determined aetiology	4 (2.6%)
Medical complications/infections during hospitalization (%)	39/32 (25.8%/21.2%)
Median time of hospitalization in days (IQR)	7 (6)
Median NIHSS at discharge (IQR)	6 (10)
Median NIHSS at 12 months (IQR)	3 (7)
mRS ≤ 2 at discharge	52 (34.4%)
mRS ≤ 2 at 6 months	71 (47.0%)
mRS ≤ 2 at 12 months	73 (48.7%)
mRS = 6	23 (15.2%)
Before the 7th day	7
Between the 7th day and the 6th month	11
Between the 6th and the 12th month	5
Imaging stroke characteristics ($n = 151$)	
Vascular territory	
ACA isolated infarct	3 (2.0%)
ACM isolated infarct	146 (96.7%)
Simultaneous ACA and ACM infarct	2 (1.3%)
Median 1st CT ASPECTS (IQR)	9 (3)
Median 1st CT Cortical ASPECTS (IQR)	6 (3)
Characteristics of isolated MCA infarct in patients with a 2nd CT scan ($n = 124$)	
Location	
Number of exclusively cortical infarct	42 (33.9%)
Number of cortico-subcortical infarct	56 (45.2%)
Number of exclusively subcortical infarct	22 (17.7%)
Median 2nd CT ASPECTS (IQR)	6 (4)
Median 2nd CT cortical ASPECTS (IQR)	4 (4)
Other features of the 2nd CT scan ($n = 129$)	
Number of patients with islands of preserved cortex within the infarct	26 (20.2%)
Number of patients with any type of haemorrhage transformation (%)	23 (17.8%)

SD standard deviation, *NIHSS* National Institutes of Health Stroke Scale score, *IQR* interquartile range, *mRS* modified Rankin Scale, *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *1st CT* 1st CT scan obtain at the emergency department, *ASPECTS* Alberta Stroke Program Early CT Score, *Cortical ASPECTS* score in ASPECTS considering only the seven cortical territories of this scale, *2nd CT* CT scan obtain ≥24 h after the infarct

Of the 144 discharged patients, 143 patients (99.3%) underwent an EEG on this date. One patient (0.7%) refused the exam. The discharge EEG was made on average 11.1 (10.9) days after stroke (median 7).

Of the 127 patients who were alive at 12 months, 117 (92.1%) performed an EEG at this time and 10 patients (7.9%) refused to repeat the exam. One patient (0.66%) was lost for clinical and neurophysiological follow-up between month 6 and 12.

Epileptic manifestations frequency

In this study, 27 patients (17.9%) had EEG epileptiform activity (interictal epileptiform activity and/or EEG seizures) during hospitalization. Table 2 shows the frequency of studied electroencephalographic abnormalities. Daily repetition of the EEG up to the 7th day after stroke allowed the identification of six more patients with EEG seizures not shown in the 1st EEG. Clinical and imagiological characteristics of patients with EEG seizures during hospitalization are displayed in supplementary file 2. NCSE was diagnosed in three out of the seven patients with EEG seizures (42.8%) and to these patients anti-epileptic drugs were prescribed. The first EEG seizure occurred until the 3rd day after stroke in 85.7% of patients (in five patients on the 2nd day and in two patients on the 3rd and 6th day after stroke, respectively).

The frequency of clinical and electroencephalographic epileptic manifestations is displayed in Table 3. One year after stroke, 23 (15.2%) patients with an acute anterior ischaemic stroke had epilepsy diagnosis criteria. Seven of these epilepsy patients (30.4%) had had an acute symptomatic seizure in the first 7 days after stroke, 2 of which (28.6%) were exclusively EEG seizures. In addition, 31.8% of patients with acute symptomatic seizures (7 out of 22) also had a remote symptomatic seizure and consequently an epilepsy diagnosis.

In the first week after stroke, four patients (2.6%) had criteria for the diagnosis of NCSE [30, 33]. In two of them, this diagnosis was made on the 1st EEG performed on the 2nd day after stroke and on other two during the first week EEG serial study (on the 3rd and the 6th day after stroke). Of the patients who met criteria for this diagnosis at the time of the 1st EEG, one had a fluctuating aphasia and periodic discharges at 3.5 Hz (aphasic focal NCSE) and another had consciousness impairment on the 2nd day after stroke, neither explained by imaging nor by medical complications and electrographic seizures, condition which reverted with antiepileptic treatment (focal NCSE with impaired consciousness). Of the two other patients that were in NCSE in the first week after stroke, 1 had repeated sensitive focal seizures, an EEG with periodic discharges at 2 Hz and electrical seizures with clinical and neurophysiological recovery after levetiracetam (focal NCSE without changing the state of consciousness). The last patient who was in NCSE during hospitalization had a malignant infarction with consciousness impairment (coma Glasgow scale score = 4) and multiple seizures in the electroencephalographic recording (NCSE with coma).

Discussion

In this work, 18% of anterior circulation ischaemic stroke patients had interictal or ictal epileptiform activity in the EEG during hospitalization and 25% at least one seizure in

Table 2 EEG abnormalities in different time frames after stroke

	1st EEG *n* (%)	Serial EEG study during hospitalization *n* (%)	Mc. Nemar's test 1 *p*	Discharge EEG *n* (%)	Mc. Nemar's test 2 *p*	12 M EEG *n* (%)	Mc. Nemar's test 3 *p*
Total of patients with	151 (100)	151 (100)	–	143 (94.7)	–	116 (76.8)	–
PD	27 (17.9)	38 (25.2)	0.007	9 (6.3)	0.002	3 (2.6)	0.002
IEA	16 (10.6)	18 (11.9)	ns	12 (8.4)	ns	5 (4.3)	ns
EEG seizures	1 (0.7)	6 (4.0)	ns	0	ns	0	ns
NCSE criteria	2 (1.3)	2 (1.3)	ns	0	ns	0	ns

1st EEG video-EEG (<60 min) performed as early as possible, in the first 72 h after admission for acute anterior circulation ischaemic stroke, *Serial EEG during hospitalization* video-EEG (<60 min) performed daily for the first 7 days after stroke (except on weekend) or if neurological worsening unexplained by medical complications and with indication for repeating the imaging exam (at least one EEG record during the hospitalization with one of the analysed features), *Mc. Nemar's test 1* Mc. Nemar's test defining the difference between 1st EEG and serial EEG during hospitalization, *Discharge EEG* video-EEG (<60 min) performed at time of clinical discharge, *Mc. Nemar's test 2* Mc. Nemar's test defining the difference between 1st EEG and discharge EEG, *12 M EEG* video-EEG (<60 min) performed at 12 months after stroke, *Mc. Nemar's test 3* Mc. Nemar's test defining the difference between 1st EEG and 12 months EEG, *PD* periodic discharges, *IEA* interictal epileptiforme activity, *EEG Seizures* electrographic seizures, *NCSE* non-convulsive status epilepticus. Four patients (2.6%) had NCSE criteria during hospitalization. Of these, three had EEG seizures and one patient periodic discharges ≥3 Hz in the 1st EEG, *ns* non-significant ($p > 0.05$)

Table 3 Frequency of clinical and EEG epileptic manifestations in anterior circulation stroke patients

Type of epileptic manifestation	*n* (%)
At least one epileptic seizure in the first year after stroke	38 (25.2%) 33 (86.8%) exclusively clinical seizures 5 (13.2%) exclusively EEG seizures
Acute symptomatic seizure (at least one)	22 (14.6%) 17 (77.3%) exclusively clinical seizures 5 (22.7%) exclusively EEG seizures 13 (59.1%) occurred in the first 24 h
Remote symptomatic seizure as the first seizure	16 (10.6%)
Remote symptomatic seizure (at least one remote symptomatic seizure, with or without a previous acute symptomatic seizure)	23 (15.2%) 7 Also acute symptomatic seizures (5 clinical and 2 EEG seizures) 11 (47.8%) between day 7 and 6th month 12 (52.2%) between the 6th and 12th month
IEA in the 1st EEG	16 (10.6%)
EEG seizure within the first 7 days of stroke	7 (4.6%)
IEA or EEG seizure during hospitalization	27 (17.9%)

EEG seizures electrographic seizures, *IEA* interictal epileptiform activity

the first year after stroke. Furthermore, more than 20% of acute symptomatic seizures were exclusively electrographic and more than 40% of patients with EEG seizures had NCSE criteria or remote symptomatic seizures. Our results support the hypothesis that in the absence of a neurophysiological evaluation, the frequency of acute symptomatic seizures after stroke is underestimated.

Several strengths are identified in this work including the sample size of anterior circulation acute stroke patients, with prospective clinical and EEG follow-up, unlike previous studies (supplementary file 3 and 4), and the small number of patients lost for clinical follow-up ($n = 1$). Another aspect that stands out is the use of internationally recognized terminology for EEG description [29]. This terminology not only shows a good inter-observer agreement [37, 38] as it is recommended for multicentric research on EEG patterns in acute neurological disease patients [37] and for implementation in clinical practice [38]. In addition, the time period for classification of seizures as acute or remote symptomatic is in accordance with the ILAE recommendations [31] and only acute anterior circulation infarcts established by imaging were included.

There are some limitations in this study. The serial and non-continuous nature of the neurophysiological assessment may in fact be considered a constraint. However, using a single EEG with less than 60 min duration we found the same percentage of patients with periodic discharges and epileptiform activity as Carrera et al. [39] in patients undergoing continued EEG monitoring for over 17 h. Thus, our work suggests that a briefer EEG, performed in a short time window after stroke, can provide similar information than a longer record, with the advantage of being technically easier and less expensive. Nevertheless, periodic discharges and epileptiform activity have different specificities in seizure prediction. Although periodic discharges have been described in the continuum between an interictal and ictal phenomenon [40], this activity may be an acute cerebral lesion signature [41]. For this reason we clearly defined and distinguished interictal epileptiform activity and periodic discharges. Nevertheless, the percentage of interictal epileptiforme activity found in our study is not to much different from Carrera et al. [39] (10.6 vs. 14%). Future studies should compare the performance of short duration (spot) EEG *versus* a continuous one in the detection of epileptic manifestations.

In our series, 22.7% of acute symptomatic seizures were exclusively electroencephalographic and occurred for the first time in the majority (85.7%) of patient in the first 72 h after stroke. An intensive care unit study, with continuous EEG also showed that 89% of seizures occurred within 72 h [42]. These observations show the importance of a neurophysiological evaluation, particularly in the first 3 days after stroke. Furthermore, in our study, almost 1/3 (31.8%) of patients having a seizure in the first seven days after stroke had an epilepsy diagnosis 1 year after stroke, in accordance to Hesdorffer et al. [2] which found a 33% risk of an unprovoked seizure in patients with a first post-stroke acute symptomatic seizure. Additionally, our results showed that more than ¼ (28,6%) of post-stroke acute symptomatic seizure patients that had a vascular epilepsy diagnosis in 1 year time period, would not have been identified without the EEG protocol that was used.

However, in our study, the frequency of EEG seizures (4.6%) is lower than that reported in continuous EEG

studies in ischaemic stroke ranging between 6 to 27% [7, 39, 42–46] (supplementary file 3). This observation was expected since, comparatively with 1st short duration EEG, a continuous record detected twice more seizures in a population of intensive care unit patients [44]. However, it is possible that the low number of patients with EEG seizures is not exclusively due to a shorter EEG duration but also to our study setting (a neurology department stroke unit) and to the inclusion of less severe stroke patients than intensive care units. Furthermore, different definitions of ictal epileptic activity can also account for the lower amount of detected EEG seizures in our study. The evidence favouring continuous *versus* spot EEG in detecting seizures is limited [47], especially in patients with ischemic stroke admitted to non intensive profile services as it was the case of our patients. Still, continuous EEG it is not accessible at all centres and its cost–benefit is not determined [48].

In our study, 42.9% of patients with EEG seizures fulfilled criteria for the diagnosis of NCSE or had remote symptomatic seizures in the clinical follow-up. In fact, non-convulsive status epilepticus has been described as one of the major diagnostic and therapeutic challenges in modern neurology [49] and the EEG is essential for its diagnosis. The described association between post-stroke status epilepticus and functional prognosis [50–52], reinforces the importance of early recognition of this entity, allowing appropriate and timely treatment. Due to very low clinical evidence, current ESO guidelines [3] only give weak recommendations on secondary prevention of acute symptomatic post-stroke seizures. Their treatment is frequently decided on an individual basis guided but the presence of intermittent or persistent altered mental status and fluctuating recovery or status epilepticus diagnosis [4]. In our study, more than 40% of patients with EEG seizures had NCSE criteria and 75% of patients with NCSE (three out four) had no obvious clinically acute post-stroke symptomatic seizures, showing the usefulness of our eletrophysiological study.

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Compliance with ethical standards

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Ethics approval This study has been approved by the Ethics Committee "Comissão de Ética para a Saúde" of the HSM-CHLN and has, therefore, been preformed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Fisher RS, Acevedo C, Arzimanoglou A et al (2014) ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia 55:475–482
2. Hesdorffer DC, Benn EKT, Cascino GD, Hauser WA (2009) Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. Epilepsia 50:1102–1108
3. Holtkamp M, Beghi E, Benninger F et al (2017) European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy. Eur Stroke J 2:103–115
4. Chung JM (2014) Seizures in the acute stroke setting. Neurol Res 36:403–406
5. Camilo O, Goldstein LB (2004) Seizures and epilepsy after ischemic stroke. Stroke 35:1769–1775
6. Pitkänen A, Roivainen R, Lukasiuk K (2015) Development of epilepsy after ischaemic stroke. Lancet Neurol 15:185–197
7. Claassen J, Mayer S, Kowalski RG et al (2004) Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 62:1743–1748
8. Huang CW, Saposnik G, Fang J et al (2014) Influence of seizures on stroke outcomes: a large multicenter study. Neurology 82:768–776
9. Young GB, Jordan KG, Doig GS (1996) An assessment of non-convulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology 47:83–89
10. Oddo M, Carrera E, Claassen J et al (2009) Continuous electroencephalography in the medical intensive care unit. Crit Care Med 37:2051–2056
11. Kamel H, Betjemann JP, Navi BB et al (2013) Diagnostic yield of electroencephalography in the medical and surgical intensive care unit. Neurocrit Care 19:336–341
12. Goldstein L, Bertels C, Davis J (1989) Interrater reliability of the NIH stroke scale. Arch Neurol 46:660–662
13. Banks JL, Marotta CA (2007) Outcomes validity and reliability of the modified rankin scale: implications for stroke clinical trials—a literature review and synthesis. Stroke 38:1091–1096
14. Rankin J (1957) Cerebral vascular accidents in patients over the age of 60: II. Prognosis. Scottish Med J 2:200–215
15. van Swieten JC, Koudstaal PJ, Visser MC et al (1988) Interobserver agreement for the assessment of handicap in stroke patients. Stroke 19:604–607
16. Adams H, Bendixen B, Kappelle L et al (1993) Classification of subtype of acute ischemic stroke. Stroke 23:35–41
17. Ottman R, Barker-Cummings C, Leibson CL et al (2010) Validation of a brief screening instrument for the ascertainment of epilepsy. Epilepsia 51:191–197
18. Nuwer M, Comi G, Emerson R et al (1998) IFCN standards for digital recording of clinical EEG. International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol 106:259–261
19. Flink R, Pedersen B, Guekht B et al (2002) Guidelines for the use of EEG methodology in the diagnosis of epilepsy. International League Against Epilepsy: commission report. Commission on European Affairs: subcommission on European Guidelines. Acta Neurol Scand 106:1–7

20. American Clinical Neurophysiology Society (2006) Guideline 4: standards of Practice in Electroencephalography. http://www.acns.org/pdf/guidelines/Guideline-4.pdf. Accessed 05 Aug 2017
21. American Clinical Neurophysiology Society (2006) Guideline 5: guidelines for standard electrode position nomenclature. Clin Neurophysiol 6:1–3
22. Martins da Silva A, Bentes C, Atalaia A, Mendes-Ribeiro JA (2011) Recomendações para utilização do electroencefalograma (EEG) em Epilepsia: Relatório à Liga Portuguesa Contra a Epilepsia. http://static.lvengine.net/epilepsia/Imgs/pages/page_105/comisso-de-eeg_lpce_v1.pdf. Accessed 05 Aug 2017
23. Alberta Health Services (2016) University of calgary medicine faculty training for aspects. http://www.aspectsinstroke.com/training-for-aspect. Accessed 10 Apr 2016
24. Barber P, Demchuk A, Zhang J, Buchan A (2000) Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 355:1670–1674
25. Anon (2002) The SITS Monitoring Study (SITS-MOST) Final protocol. http://www.acutestroke.org/SM_Protocol/SITS-MOST_final_protocol.pdf. Accessed 05 Aug 2017
26. Ryglewicz D, Baranska-Gieruszczak M, Niedzielska K, Kryst-Widzgowska T (2013) EEG and CT findings in poststroke epilepsy. Acta Neurol Scand 81:488–490
27. Awada A, Omojola MF, Obeid T (1999) Late epileptic seizures after cerebral infarction. Acta Neurol Scand 99:265–268
28. Pohlmann-Eden B, Fatar M, Hennerici M (2001) The preserved cortical island sign is highly predictive of postischemic seizures. Cerebrovasc Dis 12:282
29. Hirsch LJ, LaRoche SM, Gaspard N et al (2013) American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 30:1–27
30. Beniczky S, Hirsch LJ, Kaplan PW et al (2013) Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 54:28–29
31. Beghi E, Carpio A, Forsgren L et al (2010) Recommendation for a definition of acute symptomatic seizure. Epilepsia 51:671–675
32. Hauser WA, Beghi E (2008) First seizure definitions and worldwide incidence and mortality. Epilepsia 49:8–12
33. Trinka E, Cock H, Hesdorffer D et al (2015) A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 56:1515–1523
34. Leitinger M, Beniczky S, Rohracher A et al (2015) Salzburg consensus criteria for non-convulsive status epilepticus—approach to clinical application. Epilepsy Behav 49:158–163
35. Noachtar S, Binnie C, Ebersole J et al (1999) A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 52:21–41
36. Bentes C, Martins H, Peralta AR et al (2017) Epileptic manifestations in stroke patients treated with intravenous alteplase. Eur J Neurol 24(6):755–761
37. Gaspard N, Hirsch LJ, LaRoche SM et al (2014) Interrater agreement for critical care EEG terminology. Epilepsia 55:1366–1373
38. Leitinger M, Trinka E, Gardella E et al (2016) Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol 15:1054–1062
39. Carrera E, Michel P, Despland P et al (2006) Continuous assessment of electrical epileptic activity in acute stroke. Neurology 67:99–104
40. Chong D, Hirsch L (2005) Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. J Clin Neurophysiol 22:79–91
41. Hartings JA, Williams AJ, Tortella FC (2003) Occurrence of nonconvulsive seizures, periodic epileptiform discharges, and intermittent rhythmic delta activity in rat focal ischemia. Exp Neurol 179:139–149
42. Vespa PM, O'Phelan K, Shah M et al (2003) Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. Neurology 60:1441–1446
43. Kurtz P, Gaspard N, Wahl AS et al (2014) Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med 40:228–234
44. Pandian JD, Cascino GD, So EL et al (2004) Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit. Arch Neurol 61:1090–1094
45. Swisher CB, Shah D, Sinha SR, Husain AM (2015) Baseline EEG pattern on continuous ICU EEG monitoring and incidence of seizures. J Clin Neurophysiol 32:147–151
46. Westover MB, Shafi MM, Bianchi MT et al (2015) The probability of seizures during EEG monitoring in critically ill adults. Clin Neurophysiol 126:463–471
47. Claassen J, Vespa P (2014) Electrophysiologic monitoring in acute brain injury. Neurocrit Care 21:129–147
48. Grillo E (2015) Concerns about utility and cost-effectiveness of continuous critical-care EEG. J Clin Neurophysiol 32:442–443
49. Meierkord H, Holtkamp M (2007) Non-convulsive status epilepticus in adults: clinical forms and treatment. Lancet Neurol 6:329–339
50. Velioglu SK, Ozmenoglu M, Boz C, Alioglu Z (2001) Status epilepticus after stroke. Stroke 32:1169–1172
51. Rumbach L, Sablot D, Berger E et al (2000) Status epilepticus in stroke: report on a hospital-based stroke cohort. Neurology 54:350–354
52. Knake S, Rochon J, Fleischer S et al (2006) Status epilepticus after stroke is associated with increased long-term case fatality. Epilepsia 47:2020–2026

ORIGINAL ARTICLE

Epilepsia partialis continua after an anterior circulation ischaemic stroke

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Keywords: cerebral infarction, cortical myoclonus, *epilepsia partialis continua*, jerk-locked back averaging analysis, status epilepticus, stroke

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Background and purpose: Although cerebrovascular disorders are the main cause of *epilepsia partialis continua* (EPC) in adulthood, the frequency of EPC after stroke is unknown. The aim was to prospectively ascertain its frequency 1 year after an ischaemic stroke.

Methods: This was a prospective study of consecutive acute anterior circulation ischaemic stroke patients, previously independent, with an admission National Institutes of Health Stroke Scale score ≥4, an acute ischaemic lesion on imaging and no previous epileptic seizures. During admission patients received standardized diagnostic and medical care and were submitted to a neurophysiological evaluation protocol. One year after stroke, patients were re-evaluated by an epilepsy expert neurologist and performed a video-electroencephalogram with electromyography co-registration whenever myoclonus was observed during neurological examination for jerk-locked back averaging analysis (JLBA). EPC was defined as continuously repeated fragments of epileptic seizures, with preserved consciousness, lasting at least 1 h, and representing locally restricted epileptic activity.

Results: In all, 151 acute anterior circulation stroke patients were consecutively included and prospectively evaluated, but 23 died in the first year. One year after stroke, from 127 patients alive, 117 (92.1%) underwent clinical and neurophysiological evaluation. In two (1.7%) patients, EPC diagnosis was made both by clinical and electroencephalographic criteria, namely JLBA. Both patients had a history of remote symptomatic seizures and one of them acute symptomatic seizures and non-convulsive status epilepticus criteria during the first 7 days after stroke.

Conclusions: Despite its low frequency, the high stroke incidence makes post-stroke EPC relevant. This study draws attention to this recognizable condition with therapeutic and eventually prognostic implications.

Introduction

Cerebrovascular disorders are the main cause of *epilepsia partialis continua* (EPC) [1,2] in adulthood. However, to our knowledge, the frequency of this type of focal status epilepticus [3] as a chronic post-stroke complication in large series has not been reported. Our hypothesis is that the subtle clinical signs in motor EPC make this disorder under-recognized.

In this study, the aim is to describe the frequency of this entity 1 year after an anterior circulation ischaemic stroke.

Methods

This was a prospective study of consecutive patients admitted to our stroke unit from October 2011 to

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October 2013 with an acute anterior circulation ischaemic stroke. The Ethics Committee 'Comissão de Ética para a Saúde' of the Hospital de Santa Maria – Centro Hospitalar Lisboa Norte approved the study. Signed informed consent was obtained from all patients or their next of kin.

Patients had to be previously independent (modified Rankin Scale score <1), have an National Institutes of Health Stroke Scale score ≥4 at hospital admission and an acute anterior circulation ischaemic lesion identified by brain imaging [computed tomography (CT) or magnetic resonance imaging]. Exclusion criteria were an acute posterior circulation ischaemic stroke and a previous history of epileptic seizures, traumatic head injury requiring hospital admission or brain surgery.

Included patients were submitted to standard cerebrovascular clinical and complementary evaluation during admission and after discharge. Seizure occurrence during the first year after stroke was prospectively quantified and seizures were classified as acute [4] or remote [5] symptomatic whenever they occurred within the first 7 days after stroke or after that time point in the absence of precipitating factors, respectively.

All patients underwent a neurophysiological evaluation protocol that included a 64-channel video-electroencephalogram (EEG) with a maximum duration of 60 min in the first 72 h after stroke, during admission (daily until day 7 and after that if neurological worsening), at discharge and 1 year after stroke.

A neurologist with expertise in epilepsy (CB) made a phone interview 6 months after stroke, accessing seizure occurrence by a free interview followed by a brief phone screening tool for identifying patients with epilepsy [6], and a scheduled appointment 12 months after the cerebrovascular event. On this occasion neurological examination was always performed and special attention was given to the observation of face and limbs at rest, and to the performance of myoclonus activation manoeuvres such as posture maintaining, passive mobilization and tactile stimulation. On the same day as this appointment, a video-EEG with a sampling frequency of 1000 Hz, at least 64 channels placed according to the 10/10 international system and 60 min maximum duration was performed. Whenever myoclonus was observed during the neurological examination, a synchronized electromyography (EMG) record of the involuntary movement was added to the examination. The EEG record included eyelid opening and closure, hyperventilation, photic stimulation and manoeuvres to elicit myoclonus, as previously observed in the neurological medical evaluation. Experienced technicians under medical supervision performed the EEG. The procedure allowed subsequent offline 'jerk-lock back averaging'. This analysis was performed using the BESA software, version 6.0 (BESA GMbH, Gräfelfing, Germany) with the aim of looking for an electroencephalographic transient temporally related to the involuntary movement. The identification of a wave with a coherent focal localization and a short latency to a myoclonus burst, lasting less than 100 ms, was considered an argument for a cortical correlate of the registered myoclonus [7].

The primary outcome of this study was the presence of EPC defined as a condition of continuously repeated fragments of epileptic seizures (motor or sensory), with preserved consciousness, lasting at least 1 h, and representing locally restricted epileptic activity [8]. The presence of a cortical correlate in jerk-lock back averaging of a suspect clinical motor phenomenon was considered as evidence of motor cortex hyperexcitability, supporting the diagnosis of EPC.

Results

In all, 151 patients (112 men and 39 women) with an acute anterior circulation ischaemic stroke were included, with a mean age of 67.4 (SD 11.9) years.

In 146 patients (96.7%) the acute imaging lesion was limited to middle cerebral artery (MCA) territory and in three (2.0%) to anterior cerebral artery (ACA) territory. Furthermore, in two patients both ACA and MCA territories were involved. In a brain CT scan performed at least 24 h after stroke, the median Alberta Stroke Programme Early CT Score (ASPECTS) [9] was 6 (interquartile range 4) and the median ASPECTS considering only the seven cortical territories of this scale was 4 (interquartile range 4). ASPECTS vascular territory in patients with an infarct limited to MCA territory in brain imaging study is disclosed in Table S1.

In the first year after stroke 23 patients had died (seven during admission and 16 after discharge) and one patient was lost to follow-up after the 6-month telephone interview. At 12 months after stroke, 127 patients were alive and 117 (92.1%) agreed to come to the scheduled clinical appointment and underwent an EEG.

At the 1-year appointment, two patients (1.7%), both with previous acute and/or remote sensorimotor symptomatic seizures (Table 1), presented with continuous and subtle involuntary movements of the upper limb contralateral to the ischaemic lesion, not spontaneously reported by the patient nor their family. Several fingers showed irregular, small amplitude, non-synchronized subtle and mainly jerky movements, suggesting described central minipolymyoclonus [10]. The involuntary movement semiology is shown in Videos S1 and S2. A cortical correlate of the aforementioned involuntary movements was found by the jerk-lock back averaging

Table 1 Clinical, imaging and neurophysiological characteristics of patients with post-stroke *epilepsia partialis continua*

	Patient 1	Patient 2
Clinical features		
Age (years)	71	77
NIHSS at admission	16	7
NIHSS after intravenous alteplase	14	7
NIHSS at discharge	12	8
Stroke aetiology after investigation	Undetermined	Undetermined
Acute symptomatic seizures[a] and their type	No	Yes Focal seizures (sensory) and non-convulsive status epilepticus criteria [14]
Remote symptomatic seizures[b] and their type	Yes Focal seizures (motor) of the left upper limb	Yes Focal seizures (motor) of the left limbs during sleep
Time of the first seizure	Between 6 and 12 months	Third day after stroke
EPC semiology (12 months after stroke)	Irregular, small amplitude, non-synchronized subtle mainly jerky movements of several fingers, accentuated by posture (Video S1)	Irregular, small amplitude, non-synchronized subtle jerky movements of several fingers, accentuated by posture (Video S2)
Anti-epileptic drugs	Levetiracetam started by the time of the EPC diagnosis	Levetiracetam started during admission, dose increased after EPC diagnosis
Modified Rankin Scale score at 12 months	3	3
Brain CT scan[c] features		
Vascular territory	Right middle cerebral artery	Right middle cerebral artery
ASPECTS (total score)	3	5
ASPECTS (infarct location[d])	I, L, C, IC, M2, M3, M6	I, IC, M2, M3, M6
Any type of haemorrhage transformation	Yes	Yes
Spared cortex islands within the infarct	Yes	No
Neurophysiological features		
Raw EEG analysis (performed 12 months after stroke)	Right fronto-temporal focal and rhythmic slow wave activity No interictal epileptiform activity	Right fronto-temporal focal slow wave Activity. No interictal epileptiform activity
Jerk-locked back averaging	A negative right central electroencephalographic transient preceding muscle activation (Fig. 1a)	A negative right central electroencephalographic transient preceding muscle activation (Fig. 1b)

ASPECTS, Alberta Stroke Programme Early CT Score (quantifying infarct size and location in middle cerebral artery territory); CT, computed tomography; EEG, electroencephalogram; EPC, *epilepsia partialis continua*; NIHSS, National Institutes of Health Stroke Scale score (quantifying stroke clinical severity). [a]Seizures occurring in the first 7 days after stroke; [b]seizures occurring after the first 7 days after stroke, in the absence of precipitating factors; [c]brain CT scan performed 24 h after stroke; [d]infarct location I, insular ribbon; L, lentiform nucleus; C, caudate; IC, internal capsule; M1, anterior middle cerebral artery (MCA) cortex; M2, MCA cortex lateral to the insular ribbon; M3, posterior MCA cortex; M4, M5, M6, anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, rostral to basal ganglia.

technique (Fig. 1), adding neurophysiological criteria of EPC to clinical observation. In these patients, no epileptiform activity was detected in the raw EEG analysis. Clinical, imaging and neurophysiological characteristics as well as the treatment of patients with EPC are described in Table 1.

In our series, sensory symptoms as a manifestation of EPC were not recorded.

Discussion

In this study, the frequency of EPC as a remote complication of anterior circulation ischaemic stroke is very low. However, because stroke is a frequent neurological disorder, health professionals caring for patients with cerebrovascular disorders and aware of this disorder will find EPC in a significant number of patients.

Epilepsia partialis continua can be classified as a focal motor status epilepticus type [3], although some authors extend the meaning of EPC to cover other types of focal seizures which are continuous without spreading to a larger seizure or with only occasional spread [8]. Its physiopathology is not completely understood but the hyperexcitability of the sensorimotor cortex, the presence of cortical generators and

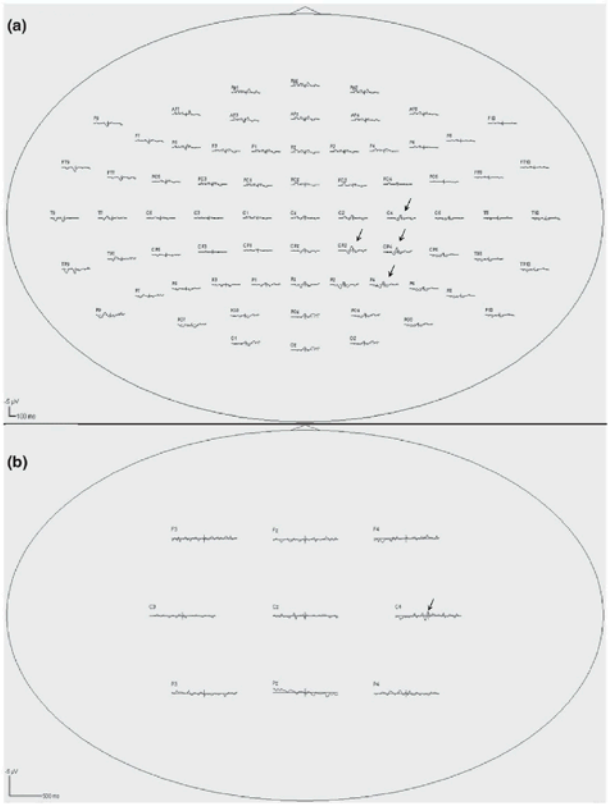

Figure 1 Jerk-locked back averaging analysis (JLBA). (a) Patient 1: JLBA analysis of 49 activations of the left flexor digitorum superficialis. There is a negative electroencephalographic transient starting 50 ms before the onset of the EMG activation (arrows). Top view of the average montage [EEG recorded with sensitivity 5 μV/mm, high frequency filter (HFF) 70 Hz, low frequency filter (LFF) 0.53 Hz, notch filter (50 Hz) on]. (b) Patient 2: JLBA of 259 activation of the left abductor pollicis brevis. There is a small amplitude negative electroencephalographic transient on the right central leads that starts 45 s before the EMG activation (arrow). Top view of the average montage (EEG recorded with sensitivity 5 μV/mm, HFF 70 Hz, LFF off, notch filter off). Montage was reduced to nine channels due to frequent artefacts in the remaining.

cortical-subcortical loops can contribute to the persistence of a focal cortical epileptiform activity [11]. The biological changes associated with post-stroke gliosis and meningocerebral cicatrix formation may result in hyperexcitability and neuronal synchrony [12] facilitating EPC.

The diagnosis of EPC frequently implies a high level of clinical suspicion and requires a careful clinical evaluation including myoclonus activation manoeuvres. In this prospective study, the subtle involuntary movements of the fingers not reported by the patient and only detected at clinical inspection, increasing with activation manoeuvres, resemble minipolymyoclonus [10]. Minipolymyoclonus of central origin was first described by Wilkins *et al.* in 1985 [10] in 11 heterogeneous patients with different types of epilepsy syndromes and neurodegenerative disorders. To our best knowledge, this paper is the first to describe this phenomenology in a prospective cohort of stroke patients.

Clinical suspicion of EPC must be corroborated by imaging and neurophysiology studies [7],

including jerk-lock back averaging analysis, as in our patients. This neurophysiological technique is of utmost importance because raw data visual analysis does not necessarily show continuous or persistent epileptiform or periodic abnormalities, such as in other types of focal or non-convulsive status epilepticus [13,14]. However, it must be reinforced that back averaging analysis only confirms the cortical origin of the involuntary movement. The clinical integration of these data is essential to the EPC diagnosis, since cortical myoclonus and minipolymyoclonus can be found in other pathologies [7,10]. The two patients of our study also had sporadic remote symptomatic non-provoked focal motor seizures supporting the diagnosis of this form of status epilepticus. In fact, the clinical phenomenology of EPC can be seen as continuously repeated fragments of motor seizures [8]. Furthermore, one of our patients had a diagnosis of non-convulsive focal status epilepticus without impairment of consciousness in the first week after stroke.

It should also be emphasized that, in stroke patients, involuntary movements can be caused by different mechanisms and that post-stroke focal myoclonus can additionally be a hyperkinetic movement disorder, where basal ganglia are most often involved. Although lesions in different parts of the brain can cause the same movement disorder, post-stroke myoclonus is usually associated with lesions in the midbrain, pons or thalamus and is frequently an acute stroke complication [15,16]. This was not the case for our patients. Furthermore, an involuntary movement cortical correlate was established in this work by back averaging analysis.

Regarding the treatment of EPC, studies that included patients with ischaemic stroke as the aetiology show the use of different anti-epileptic drugs and variable clinical response, frequently requiring polytherapy or even being refractory [1,2]. As in our study, the study by Mameniskiene *et al.* [8] showed that the control of EPC did not always correlate with control of other types of seizures in the same patient.

The consequences of post-stroke EPC are unknown although post-stroke epileptic phenomena (seizures and status epilepticus) [17–21] have been associated with a worse infarct outcome.

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Disclosure of conflicts of interest

Dr Bentes received the 2012 Research Grant in Cerebrovascular Diseases (Scientific Promoter: Sociedade Portuguesa do AVC/Sponsor: Tecnifar). Dr Ferro reports personal fees from Boehringer Ingelheim outside the submitted work. The remaining authors have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. ASPECTS vascular territory in patients with an infarct limited to middle cerebral artery territory in brain imaging study.

Video S1. Irregular, small amplitude, non-synchronized subtle mainly jerky movements of several fingers of patient 1, accentuated by posture, are observed.

Video S2. Irregular, small amplitude, non-synchronized subtle jerky movements of several fingers of patient 2 are observed.

References

1. Cockerell OC, Rothwell J, Thompson PD, Marsden CD, Shorvon SD. Clinical and physiological features of epilepsia partialis continua. Cases ascertained in the UK. *Brain* 1996; **119:** 393–407.
2. Sinha S, Satishchandra P. Epilepsia partialis continua over last 14 years: experience from a tertiary care center from south India. *Epilepsy Res* 2007; **74:** 55–59.
3. Trinka E, Cock H, Hesdorffer D, *et al.* A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; **56:** 1515–1523.
4. Beghi E, Carpio A, Forsgren L, *et al.* Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 2010; **51:** 671–675.
5. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* 2008; **49** (Suppl. 1)**:** 8–12.
6. Ottman R, Barker-Cummings C, Leibson CL, Vasoli VM, Hauser WA, Buchhalter JR. Validation of a brief screening instrument for the ascertainment of epilepsy. *Epilepsia* 2010; **51:** 191–197.
7. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004; **3:** 598–607.
8. Mameniskiene R, Bast T, Bentes C, *et al.* Clinical course and variability of non-Rasmussen, nonstroke motor and sensory epilepsia partialis continua: a European survey and analysis of 65 cases. *Epilepsia* 2011; **52:** 1168–1176.
9. Barber P, Demchuk A, Zhang J, Buchan A. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta

Stroke Programme Early CT Score. *Lancet* 2000; **355:** 1670–1674.
10. Wilkins DE, Hallett M, Erba G. Primary generalised epileptic myoclonus: a frequent manifestation of minipolymyoclonus of central origin. *J Neurol Neurosurg Psychiatry* 1985; **48:** 506–516.
11. Guerrini R. Physiology of epilepsia partialis continua and subcortical mechanisms of status epilepticus. *Epilepsia* 2009; **50**(Suppl. 1)**:** 7–9.
12. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. *Stroke* 2004; **35:** 1769–1775.
13. Beniczky S, Hirsch LJ, Kaplan PW, *et al*. Unified EEG terminology and criteria for nonconvulsive status epilepticus. *Epilepsia* 2013; **54**(Suppl. 6)**:** 28–29.
14. Leitinger M, Beniczky S, Rohracher A, *et al*. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus – approach to clinical application. *Epilepsy Behav* 2015; **49:** 158–163.
15. Bansil S, Prakash N, Kaye J, *et al*. Movement disorders after stroke in adults: a review. *Tremor Other Hyperkinet Mov (N Y)* 2012; **2:** tre-02-42-195-1.
16. Mehanna R, Jankovic J. Movement disorders in cerebrovascular disease. *Lancet Neurol* [Internet] 2013; **12:** 597–608.
17. De Reuck J, Claeys I, Martens S, *et al*. Computed tomographic changes of the brain and clinical outcome of patients with seizures and epilepsy after an ischaemic hemispheric stroke. *Eur J Neurol* 2006; **13:** 402–407.
18. Huang CW, Saposnik G, Fang J, Steven DA, Burneo JG. Influence of seizures on stroke outcomes: a large multicenter study. *Neurology* 2014; **82:** 768–776.
19. Arntz RM, Rutten-Jacobs LCA, Maaijwee NAM, *et al*. Poststroke epilepsy is associated with a high mortality after a stroke at young age. *Stroke* 2015; **46:** 2309–2311.
20. Rumbach L, Sablot D, Berger E, Tatu L, Vuillier F, Moulin T. Status epilepticus in stroke: report on a hospital-based stroke cohort. *Neurology* 2000; **54:** 350–354.
21. Knake S, Rochon J, Fleischer S, *et al*. Status epilepticus after stroke is associated with increased long-term case fatality. *Epilepsia* 2006; **47:** 2020–2026.

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Case Report

Cortical myoclonus during IV thrombolysis for ischemic stroke

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ABSTRACT

We describe a patient with an acute middle cerebral artery ischemic stroke developing subtle involuntary movements of the paretic upper limb with cortical origin during rt-PA perfusion. Despite the multiple potential pathophysiological mechanisms for the relationship between thrombolysis and epileptic activity, seizures during this procedure are scarcely reported. Our hypothesis is that subtle and transient clinical seizures, like those described in our patient, may not be detected or are misdiagnosed as nonepileptic involuntary movements. We aimed to draw attention to the recognition challenge of this paroxysmal motor behavior, highlighting this clinical and neurophysiological identification using video recording and back-average analysis of the EEG.

1. Introduction

Early poststroke seizures (i.e. occurring within one week after stroke) are thought to result from cellular biochemical dysfunction leading to electrically irritable cerebral tissue. Intravenous thrombolysis (IVT) with recombinant tissue-type plasminogen activator (rt-PA) is the gold standard treatment for acute ischemic stroke, and, recently, Alvarez et al., [1] showed that this procedure may be independently associated with early seizures. However, and despite multiple potential pathophysiological mechanisms, seizures coincident with rt-PA administration are seldom reported. Here, we describe a patient with an acute middle cerebral artery (MCA) ischemic stroke who developed subtle involuntary movements of the paretic upper limb, with cortical origin as documented neurophysiologically, during rt-PA perfusion. We aimed to draw attention to the recognition challenge of this paroxysmal motor behavior, highlighting its clinical and neurophysiological identification using video recording and back-average analysis of the EEG.

2. Case report

A 72-year-old male with a past history of hypertension, dyslipidemia, chronic kidney disease, and an ischemic stroke 15 years ago, with no poststroke seizures and from which he had completely recovered, presented to the emergency department with sudden onset of left central facial palsy, hemiparesis, homonymous hemianopsia, and right gaze deviation (NIHSS score = 10). Electrocardiogram showed atrial fibrillation, and blood analysis revealed acute renal failure (creatinine = 4 mg/dL, blood urea nitrogen = 134 mg/dL). Plain head computed tomography (CT) disclosed old occipital, parietal, and frontal ischemic lesions and a right middle cerebral artery (MCA) hyperdensity. Intravenous recombinant tissue-type plasminogen activator (rt-PA) was started 140 min after symptom onset. Twenty minutes after starting the infusion period, involuntary movements of the upper paretic limb were noticed. The movements involved either the distal or the proximal muscles, independently, and could be jerk-like, irregular, myoclonic-like, or slow and brief (Video). During rt-PA perfusion, a 72-channel EEG (International 10/10 System) with an EMG channel recording the left flexor digitorum superficialis (sample frequency of 1000 Hz) captured brief, repetitive, and almost periodic muscle activations (Fig. 1A). No epileptiform activity was apparent in the raw EEG data. Back-average analysis of the EEG time-locked with the onset of the recorded myoclonus (538 activations) was performed (BESA software, version 6.0), revealing a right frontocentral negative wave. This EEG transient preceded muscle activation by 30 ms (Fig. 1B). No antiepileptic drug was given, and the involuntary movements lasted approximately 40 min, stopping by the end of the rt-PA perfusion. The neurological deficit did not improve after thrombolysis. Transcranial Doppler showed no recanalization. Computed tomography at 24 h disclosed an acute MCA infarct scoring 5 on ASPECTS, with spared cortical areas within the infarct zone

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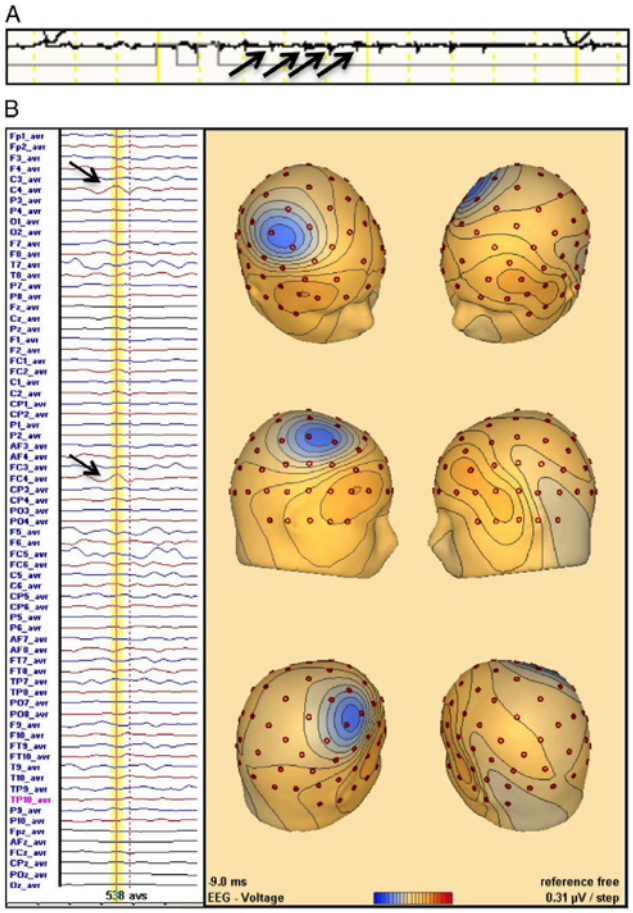

Fig. 1. A) EMG channel recording the left flexor digitorum superficialis capturing brief, repetitive, and almost periodic muscle activations (arrows). B) EEG back-average analysis disclosing a negative transient (arrows) with a peak (yellow line) of 10 ms before EMG activations (dotted line) at right central electrodes (C4/FC4).

(Fig. 2). The patient partially recovered after 7 days (NIHSS score = 6). No further involuntary movements or clinically suspected seizures were observed despite transitory worsening of renal function during hospitalization. One year after stroke, the patient is alive and independent (NIHSS = 1 and mRS = 1), with no report of late poststroke seizures.

3. Discussion

We report a patient with an acute MCA ischemic stroke who developed subtle involuntary movements of the paretic upper limb, with cortical origin as documented neurophysiologically, during rt-PA perfusion. Because cortical myoclonus and epileptogenic discharges are generated by neuronal hypersynchronous activities sharing the same physiopathogenic mechanisms, the recorded myoclonus can be considered an acute symptomatic seizure. Because of the subtleness of the movements, the clinical stability of the patient, and the absence of clear epileptiform activity on the immediate raw EEG analysis, no antiepileptic medication was given. Back-average analysis, enlightening the cortical origin of the myoclonus, was only performed after the acute phase.

Even though our patient had multiple risk factors for seizures (acute renal lesion, acute anterior stroke, cortical involvement), the close time relationship of this paroxysmal motor behavior with the therapeutic intervention raises the possibility of an association. It has been documented that seizures during rt-PA perfusion can occur even in the absence of a cerebral lesion, as described in 2 patients submitted to thrombolysis for acute myocardial infarction [2]. In fact, neurotoxic and epileptogenic properties [3] of rt-PA are known. Other postulated mechanisms for seizures during thrombolysis for ischemic stroke include secondary cortical infarct from distal embolization or reperfusion/hyperperfusion syndrome [4].

Despite the multiple potential pathophysiological mechanisms for the relationship between rt-PA and seizures, the frequency of seizures during thrombolysis is not well known. Besides a few reports of overt seizures occurring in close proximity to rt-PA perfusion [2,3], most

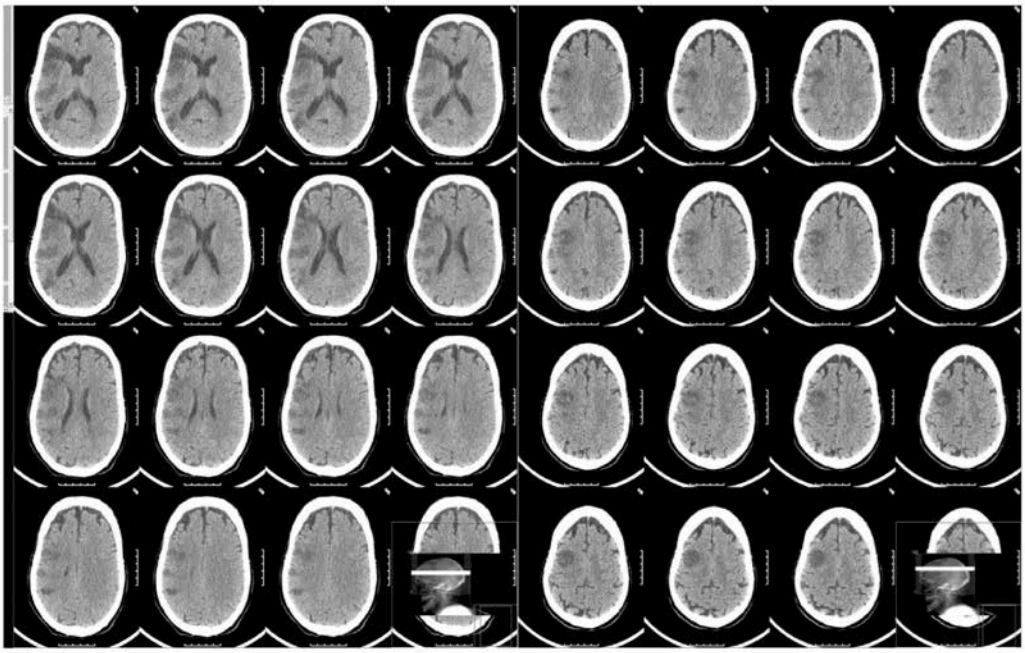

Fig. 2. Plain head CT scan 24 h after thrombolysis disclosing an acute right MCA infarct, scoring 5 (I, M1, M2, M5, M6) on ASPECTS score, with spared cortical areas within the infarct zone.

larger studies looking at seizure frequency in patients submitted to thrombolysis report a global incidence of seizures within 7 days after stroke and not specifically during the therapeutic procedure. In these studies, patients submitted to thrombolysis have similar frequency of early seizures when compared with patients without thrombolysis. Only one study concluded that thrombolysis is an independent risk factor for early seizures after stroke [1]. These discrepancies may be related to the retrospective collection of the data. Additionally, reporting bias due to increased clinical vigilance in the acute phase of patients undergoing thrombolysis cannot be excluded. Finally, it is also possible that subtle and transient clinical seizures, like those described in our patient, may not be detected or are misdiagnosed as nonepileptic involuntary movements.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebcr.2014.09.004.

Statement and acknowledgment

This clinical case is included in the project "EEG in Cerebrovascular Disease" approved by the ethics committee of our hospital. All the persons included in this study gave their informed consent to their inclusion.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

[1] Alvarez V, Rossetti AO, Papavasileiou V, Michel P. Acute seizures in acute ischemic stroke: does thrombolysis have a role to play? J Neurol 2013;260(1):55–61. http://dx.doi.org/10.1007/s00415-012-6583-6.

[2] Hafeez F, Razzaq Ma, Levine RL, Ramirez MAN. Reperfusion seizures: a manifestation of cerebral reperfusion injury after administration of recombinant tissue plasminogen activator for acute ischemic stroke. J Stroke Cerebrovasc Dis 2007;16(6):273–7. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2007.07.007.

[3] Iyer aM, Zurolo E, Boer K, Baayen JC, Giangaspero F, Arcella A. Tissue plasminogen activator and urokinase plasminogen activator in human epileptogenic pathologies. Neuroscience 2010;167(3):929–45. http://dx.doi.org/10.1016/j.neuroscience.2010.02.047.

[4] Rodan LH, Aviv RI, Sahlas DJ, Murray BJ, Gladstone JP, Gladstone DJ. Seizures during stroke thrombolysis heralding dramatic neurologic recovery. Neurology 2006;67(11):2048–9. http://dx.doi.org/10.1212/01.wnl.0000247231.25231.2e.

ORIGINAL ARTICLE

Epileptic manifestations in stroke patients treated with intravenous alteplase

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Background and purpose: Intravenous alteplase (rtPA) may be associated with seizures and epileptic activity in the electroencephalogram (EEG). The aim of this work was to compare the frequency of seizures and EEG abnormalities between stroke patients treated and not treated with rtPA.

Methods: This was a prospective study of consecutive acute anterior circulation ischaemic stroke patients, with 1-year follow-up. Patients were previously independent, had an admission National Institute of Health Stroke Scale score ≥4, an acute ischaemic lesion and no previous seizures. They received standardized diagnostic and medical care. A video-EEG was performed in 72 h (first EEG); during admission (daily until day 7 and after that if neurological worsening); at discharge and 1 year after stroke.

Results: In all, 151 patients (101 treated with rtPA) were included. The frequency of acute and remote symptomatic seizures was not significantly different between rtPA treated and non-treated patients ($P = 0.726$ and $P = 0.748$, respectively). Clinical paroxysmal phenomena during rtPA perfusion were observed in five (5%) patients. In the first EEG, rtPA treated patients more often had background diffuse slowing (43.6% vs. 26.0%, $P = 0.036$). This difference was no longer observed at discharge (24.0% vs. 19.1%, $P = 0.517$) nor 1 year after (11.8% vs. 10.0%, $P = 0.765$). No differences were found in the frequency of epileptiform ($P = 0.867$) or periodic discharges ($P = 0.381$).

Conclusions: Intravenous alteplase is not associated with an increased risk of clinical or electroencephalographic epileptic phenomena.

Introduction

Thrombolysis is the gold standard of acute ischaemic stroke treatment. However, it has been suggested that intravenous alteplase (rtPA) is associated with clinical seizures and the occurrence of epileptic activity in the electroencephalogram (EEG) [1,2]. Several physiopathological mechanisms can be postulated for this association, including cortical reperfusion/hyperperfusion syndrome [3], neurotoxicity and a possible epileptogenic effect of rtPA [3–6], or the survival of islands of cortical viable tissue [7]. rtPA related seizures [3,8,9] and seizure frequency in patients treated with rtPA [10,11] have been mostly described using retrospective and non-controlled case series. Furthermore, the occurrence of seizures in rtPA patients has been associated with different stroke functional outcomes [1,3,10–12].

The aim was to compare seizure frequency and EEG abnormalities between anterior circulation ischaemic stroke patients treated and not treated with rtPA and to know whether post-stroke seizures are associated with functional outcome in these patients.

Methods

This was a prospective longitudinal study of consecutive adult patients with an acute anterior circulation ischaemic stroke admitted to the Neurology

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Department Stroke Unit of a University Hospital between October 2011 and October 2013 and followed for 12 months. The Ethics Committee 'Comissão de Ética para a Saúde' of the Hospital de Santa Maria - Centro Hospitalar Lisboa Norte approved this study.

Included patients had to be previously independent [modified Rankin Scale (mRS) ≤ 1], score a value of at least 4 on the National Institute of Health Stroke Scale (NIHSS) upon admission to the emergency department, have had an acute ischaemic brain lesion in the internal carotid artery territory [in the computed tomography (CT) scan or magnetic resonance imaging (MRI)] and have no previous history of epileptic seizures or traumatic head injury requiring hospital admission. All subjects or their next of kin gave written informed consent for participation in the study. Patients were treated with rtPA according to European Stroke Organization (ESO) guidelines [13]. Patients were not submitted to rtPA treatment if outside the 4.5 h time window, in the presence of minor stroke (NIHSS < 4) or if showing contraindications to this drug. All patients received a standardized cerebrovascular disease investigation and medical care during admission and after discharge. A neurologist with expertise in epilepsy (CB), blinded to the neurophysiological evaluation, conducted a phone interview at 6 months after stroke accessing seizure occurrence by a free interview, followed by a brief phone screening tool for identifying patients with epilepsy [14]. A scheduled clinical appointment 12 months after stroke was also conducted (CB), recording the following clinical variables: NIHSS and mRS score, occurrence of seizures and their type; other stroke or medical complications; final aetiological classification of stroke [15] and ongoing therapy.

Neurophysiological evaluation

All patients underwent a neurophysiological evaluation protocol that included a 64 channel video-EEG with a maximum duration of 60 min at different time frames after stroke: in the first 72 h (first EEG), daily in the first 7 days after stroke, during admission after that time point if there was neurological worsening unexplained by medical complications, at discharge and 12 months after stroke.

The record included an eye closed wake resting condition and eye open, hyperventilation and photic stimulation manoeuvres. The EEG review and classification was performed by a certified clinical neurophysiologist (CB) using international criteria and terminology [16–18], blinded for clinical and imaging findings. All doubts were decided by consensus with another clinical neurophysiologist (ARP).

Imaging interpretation

Two senior neuroradiologists (CM and CC), blinded for clinical and EEG findings, reviewed all imaging tests. Doubts were decided by consensus. In patients with an infarct limited to the middle cerebral artery (MCA) territory in the imaging study (considering first CT scan, second CT scan or MRI), the infarct size was quantified by the Alberta Stroke Program Early CT Score (ASPECTS) [19] in a repeated brain CT scan performed 24 h after stroke (second CT scan). ASPECTS in the second CT scan was rated as 10 whenever an acute vascular lesion in the MCA territory was only identified by MRI.

Predictors and outcomes

The following characteristics were compared between patients treated and not treated with rtPA.

1 Demographic and stroke characteristics: age, gender, NIHSS score [20] on admission and post-rtPA (if applicable) and stroke aetiology [15]
2 Imaging characteristics: exclusively cortical and subcortical infarct, ASPECTS [19], presence of normal attenuation coefficient cortical areas (islands of preserved cortex) within the infarct [7] and any intracerebral haemorrhage transformation [21]. Insula and M1 to M6 ASPECTS territories were considered 'cortical territories of ASPECTS'
3 Occurrence of epileptic seizures and status epilepticus (only the first event was considered), with the following operational definitions:
  3.1 Epileptic seizure: clinical [22] and/or electrographic seizure [17,18]
  3.2 Acute symptomatic seizure: seizure occurring within the first 7 days of a stroke [23]. In these patients, cut-off values for metabolic disorders and febrile symptomatic seizures were not overreached and alcohol/drug withdrawal or intoxication [23] were excluded
  3.3 Remote symptomatic seizure: seizures occurring after 7 days of a stroke in the absence of precipitating factors [24]
  3.4 Status epilepticus: International League Against Epilepsy (ILAE) status epilepticus classification [25] and Salzburg Consensus Criteria for Non-convulsive Status Epilepticus [18,26] were used
4 EEG abnormalities:
  4.1 In the first EEG: background activity slowing [16]; asymmetry [17]; suppression (focal, hemispheric or diffuse) [17]; focal slow wave activity, including focal and regional concept [16]; rhythmic slow wave activity, including rhythmic delta activity defined by American Clinical

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FULL-LENGTH ORIGINAL RESEARCH

Early EEG predicts poststroke epilepsy

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Summary

Objective: Electroencephalography (EEG) can identify biomarkers of epileptogenesis and ictogenesis. However, few studies have used EEG in the prediction of poststroke seizures. Our primary aim was to evaluate whether early EEG abnormalities can predict poststroke epilepsy.

Methods: A prospective study of consecutive acute anterior circulation ischemic stroke patients, without previous epileptic seizures, who were admitted to a stroke unit over 24 months and followed for 1 year. All patients underwent standardized clinical and diagnostic assessment during the hospital stay and after discharge. Video-EEG was performed in the first 72 h (first EEG), daily for the first 7 days, in case of neurological deterioration, at discharge, and at 12 months after stroke. The occurrence of epileptic seizures in the first year after stroke (primary outcome) was evaluated clinically and neurophysiologically during the hospital stay and at 12 months. A telephone interview was also performed at 6 months. The primary outcome was the occurrence of at least one unprovoked seizure (poststroke epilepsy). Secondary outcomes were the occurrence of at least one acute symptomatic seizure and (interictal and/or ictal) epileptiform activity on at least one EEG during the hospital stay for acute stroke. The first EEG variables were defined using international criteria/terminology. Bivariate and multivariate analyses with adjustment for age, admission National Institutes of Health Stroke Scale (NIHSS) score, and Alberta Stroke Program Early CT Score (ASPECTS) were performed.

Results: A total of 151 patients were included; 38 patients (25.2%) had an acute symptomatic seizure and 23 (16%) had an unprovoked seizure.The first EEG background activity asymmetry and first EEG with interictal epileptiform activity were independent predictors of poststroke epilepsy during the first year after stroke ($P = 0.043$ and $P = 0.043$, respectively). No EEG abnormality independently predicted acute symptomatic seizures. However, the presence of periodic discharges on the first EEG was an independent predictor of epileptiform activity ($p = 0.009$) during the hospital stay.

Significance: An early poststroke EEG can predict epilepsy in the first year after stroke, independently from clinical and imaging-based infarct severity.

KEY WORDS: Ischemic stroke, Epileptic seizures, Prediction, EEG.

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KEY POINTS

- An early poststroke EEG with background activity asymmetry independently predicted epilepsy in the first year after stroke
- An early poststroke EEG with interictal epileptiform activity independently predicted epilepsy in the first year after stroke
- An early poststroke EEG with lateralized periodic discharges independently predicted the occurrence of EEG epileptiform activity during the hospital stay for acute stroke
- Our data add neurophysiological risk factors to poststroke epilepsy
- Our findings might help to identify patients with an increased risk for poststroke epilepsy

Clinical stroke severity and infarct dimension are known risk factors for poststroke epileptic seizures and vascular epilepsy.[1] Although electroencephalography (EEG) is a sensitive neurophysiological technique in the detection of acute cerebral ischemia[2] and a robust one in the functional assessment of the brain,[3] it is unclear whether electroencephalographic markers of acute vascular injury severity are independently associated with an increased risk of poststroke seizures or useful for their prediction. A single retrospective study[4] showed an association between diffuse EEG background slowing in acute stroke phase and seizure occurrence. Furthermore, although the presence of periodic discharges and frontal intermittent rhythmic delta activity has been associated with the occurrence of acute symptomatic seizures,[4] it is still unknown whether electroencephalographic markers of cortical hypersynchronization and of an epileptogenic zone may be helpful in the prediction of unprovoked seizures or poststroke epilepsy, according to the current definition.[5]

Our primary aim was to investigate whether early EEG abnormalities are independent predictors of poststroke epilepsy.

METHODS

Ours was a prospective study of consecutive patients with an acute anterior circulation ischemic stroke, admitted to the stroke unit of a neurology department between October 2011 and October 2013 and followed for 12 months. The ethics committee "Comissão de Ética para a Saúde" of the Hospital de Santa Maria - Centro Hospitalar Lisboa Norte approved this study (HSM-CHLN).

The following inclusion criteria were used: (1) Acute anterior circulation ischemic stroke, established by imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]), with fewer than 7 days of clinical evolution

(2) National Institutes of Health Stroke Scale (NIHSS) score ≥4 upon admission to the emergency department
(3) Signed informed consent by the patients or their next of kin.

The subsequent exclusion criteria were used:
(1) Posterior circulation vascular syndrome,[6] even if not confirmed by imaging
(2) Acute posterior circulation ischemic stroke, established by imaging (CT scan or MRI) obtained at any time during the hospital stay
(3) Previous stroke with modified Rankin scale (mRS) score[7] >1 at the time of acute stroke
(4) Brain imaging study (any CT scan or MRI) with one of the following: contusion, subdural/epidural hematoma, subarachnoid hemorrhage, neoplastic lesion, infectious/inflammatory lesion, or hydrocephalus
(5) Brain CT scan performed in the emergency department (first CT scan) showing intracerebral hemorrhage
(6) Previous history of head trauma with hospital admission
(7) Previous neurosurgery
(8) Previous history of epilepsy or epileptic seizures

Standardized clinical and ancillary evaluation

All patients were attended by a neurologist at the emergency department and admitted to our stroke unit with continuous surveillance of their neurological status and daily observation by a stroke neurologist. During the study period, this unit admitted all patients treated with intravenous alteplase (rtPA) in our hospital (according to European Stroke Organisation (ESO) Guidelines[8]) and, depending on bed availability, also patients not treated with rtPA. The NIHSS score and seizure occurrence were prospectively recorded. During the hospital stay, the patient underwent diagnostic tests allowing stroke etiological classification[9] and appropriate therapeutic approach, including blood tests, carotid and vertebral duplex scans, transcranial Doppler, and electrocardiography (ECG). All patients underwent a CT scan at the emergency department (first CT scan), which was repeated 24 hours after stroke in patients administered rtPA and when clinically indicated in all patients (second CT scan). Select patients also underwent MRI with diffusion-weighted imaging, transthoracic or transesophageal echocardiography, 24-hour Holter monitoring, or cerebral angiography.

After discharge, patients had a standard clinical follow-up at the cerebrovascular outpatient clinic. A neurologist with expertise in epilepsy (CB) performed a telephone interview 6 months after stroke accessing seizure occurrence, with a free interview followed by a brief phone screening tool for identifying patients with epilepsy.[10] A scheduled appointment 12 months after stroke was also conducted (CB), recording the following clinical variables: NIHSS and mRS scores, occurrence of seizures and type, other stroke or medical complications, final etiological classification of stroke,[9] and ongoing therapy.

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Neurophysiological evaluation

All patients underwent a neurophysiological evaluation protocol,[11] which included a 64-channel synchronized video-EEG with a maximum duration of 60 minutes in different time frames after stroke:

(1) As early as possible, in the first 72 hours after admission (first EEG)
(2) Daily, after the first EEG, for the first 7 days after stroke (except on weekends)
(3) If neurological worsening, unexplained by medical complications, and with indications for repeating the imaging exam
(4) At the time of clinical discharge (discharge EEG)
(5) At 12 months after stroke (12M EEG)

Imaging Interpretation

All imaging evaluations performed during the study period were reviewed by 2 senior neuroradiologists (CM and CC), who were blinded to the clinical and electroencephalographic findings and trained for Alberta Stroke Program Early CT Score (ASPECTS) classification. Doubts were discussed and final determination was reached by consensus.

In patients with an infarct limited to the middle cerebral artery (MCA) territory in the imaging study (considering first CT scan, second CT scan, or MRI), the infarct size was quantified by ASPECTS[12] in the first and second CT scan. Insula and M1 to M6 ASPECTS territories were considered "cortical territories of ASPECTS." Furthermore, any type of hemorrhage transformation,[13] cortical or subcortical infarct location, or presence of cortical areas with normal attenuation coefficient (islands of preserved cortex) within the infarct[14–16] were evaluated on the second CT.

Outcomes

The primary outcome of this study was the occurrence of at least one unprovoked epileptic seizure (poststroke epilepsy[5,17]), 1 year after stroke.

The secondary outcomes were the occurrence of at least one acute symptomatic seizure and EEG epileptiform activity on at least one EEG during the hospital stay.

The following operational definitions were used:

(1) Unprovoked seizures (or poststroke epilepsy[5,17]): at least one clinical seizure[5] occurring 7 days after (and in the first year of) a stroke, in the absence of precipitating factors[18]
(2) Acute symptomatic seizure: at least one epileptic seizure occurring within the first 7 days of a stroke.[18] In these patients, cut-off values for metabolic disorders and febrile symptomatic seizures were not overreached and alcohol/drug withdrawal or intoxication[18] were excluded
(3) Electrographic seizure; generalized spike-wave discharges at 3 per second or faster or clearly evolving discharges of any type that reach a frequency >4 per second, whether focal or generalized.[19] Evolving was defined as at least 2 unequivocal sequential changes in frequency, morphology, or location lasting for at least 3 cycles each. Evolution in frequency was defined as at least 2 consecutive changes in the same direction by at least 0.5 per second. Evolution in morphology was defined as at least 2 consecutive changes to a novel morphology. Evolution in location was defined as sequentially spreading into or sequentially from at least 2 different standard 10–20 electrode locations and persisting for at least 3 cycles.[19]
(4) EEG epileptiform activity during hospital stay (interictal or ictal): At least one EEG during hospital stay with interictal epileptiform activity (IEA)[20] and/or an electrographic seizure.[19]

Predictors

The following characteristics were studied:

(1) Clinical characteristics: age, admission NIHSS,[21] and Trial of Org 10172 in Acute Stroke Treatment classification subgroups[9]
(2) Imaging characteristics: first CT ASPECTS[12] (and cortical territories of ASPECTS), second CT with islands of preserved cortex within the infarct[14–16] (Figure 1), and any intracerebral haemorrhage[13]
(3) First EEG abnormalities: background activity slowing[20]; asymmetry[19]; suppression (focal, hemispheric or diffuse)[19]; nonrhythmic slow wave activity[20] (NRSA) defined as continuous or intermittent slow activity, that is, theta and/or delta band activity without an approximately constant period, limited to an area of the brain or scalp region (including focal and regional concept of the International Federation of Clinical Neurophysiology[20]); rhythmic slow-wave activity (RSA), including the lateralized rhythmic delta activity (LRDA) definition by the American Clinical Neurophysiology Society[19] and rhythmic delta/theta (>0.5 Hz) activity,[22] interictal epileptiform activity (IEA)[20]; lateralized periodic discharges (LPDs)[19]; electrographic seizure.[19]

Statistical analysis

A descriptive analysis was used for nominal qualitative and quantitative variables. Nominal variables are expressed in frequency, discrete variables as medians and interquartile ranges (IQRs), and continuous variables as means and standard deviations (SDs).

The bivariate analysis of qualitative variables was performed by χ^2 test, Fisher's exact test, or McNemar test and of quantitative variables by Student's *t*-test or Mann-Whitney *U* tests, as appropriate.

Variables with a significant association in bivariate analysis were adjusted in a logistic regression model for known functional outcome predictors of stroke and poststroke seizures,[1,12,23–25] namely age, clinical stroke severity (admission NIHSS), and imaging infarct size (ASPECTS), when meeting the requirements for this analysis. The

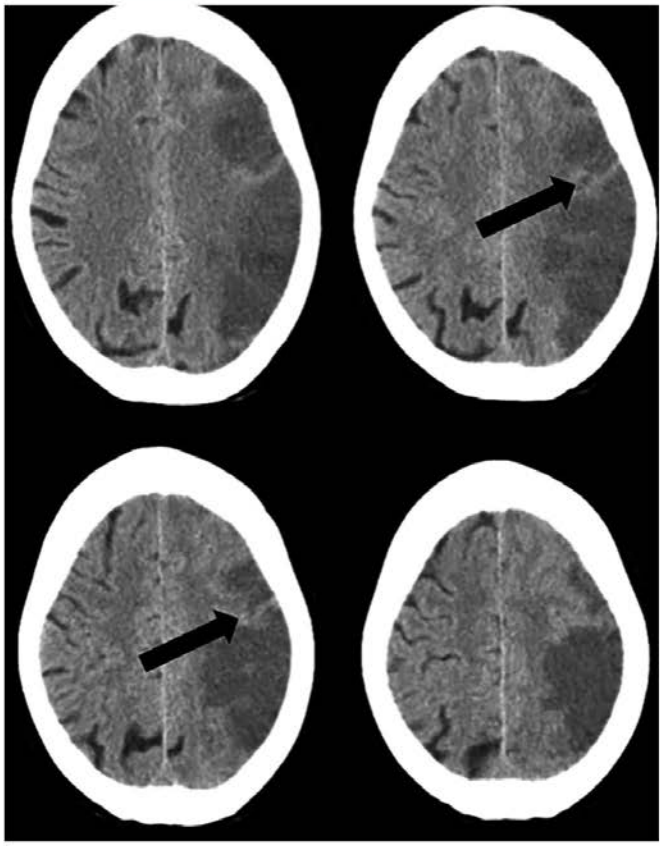

Figure 1.
Islands of preserved cortex within the infarct. Brain CT scan showing an acute left middle cerebral artery ischemic stroke. Black arrows indicate cortical areas with normal attenuation coefficient (islands of preserved cortex) within the infarct.
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significance level was $\alpha < 0.05$. The odds ratios (ORs) and the confidence intervals (CIs) of 95% were calculated.

Defined outcome prediction model characteristics encompassing predictors with the highest odds to impact outcome were studied. The percentage of patients correctly identified by the models was calculated. Model calibration was analyzed by the Hosmer-Lemeshow test, and its discriminative capacity measured by the area under the receiver-operator characteristic (ROC) curve. In all models, the study of the assumptions associated with logistic regression showed the existence of a multicollinearity problem between the variables "ASPECTS" and "cortical territories of ASPECTS". Only the first was included in the logistic regression models.

Statistical analysis was done using SPSS program version 24 for the Mac.

Results

A total of 151 patients (112 male) with a mean age of 67.4 (SD 11.9) years was included. The study flowchart was described previously.[26] The median NIHSS score was 12 (IQR 10) at admission.

An infarct limited to the MCA territory was observed in 146 patients (96.7%) and to the anterior cerebral artery (ACA) territory in 3 patients (2.0%). Two patients had MCA and ACA infarcts simultaneously. Patients with an exclusively MCA infarct had a median first CT ASPECTS

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score of 9 (IQR 3), scoring 6 (IQR 3) in the cortical territories of this scale.

All patients had at least one EEG during the hospital stay in a median time of 1 day (IQR 1) after stroke (first EEG). The median number of EEGs performed per patient was 5 (IQR 3).

Seven patients died during their hospital stay. Of the 144 discharged patients, 143 patients (99.3%) had an EEG on the date of discharge. One patient (0.7%) refused to undergo EEG. The discharge EEG was done a median of 7 days after stroke.

Of the 127 patients who were alive at 12 months, 117 (92.1%) had an EEG at this time and 10 patients (7.9%) refused to undergo the EEG. One patient (0.66%) was lost to clinical and neurophysiological follow-up between months 6 and 12.

The frequency of EEG abnormalities is described in Table 1. Clinical and imaging characteristics associated with early EEG abnormalities are described in Appendix S1. In the first 7 days after stroke, 7 patients had at least one electroencephalographic seizure (5 of whom had exclusively electrographic seizures and 2 of whom had both clinical and electrographic seizures). Clinical, imaging characteristics, and EEG abnormalities associated with these events are disclosed in Appendix S2.

During the study period, 38 patients (25.2%) had at least one epileptic seizure, 22 (14.6%) an acute symptomatic seizure, and 23 (16%) an unprovoked seizure. Furthermore, 5 patients had pure electrographic seizures during their hospital stay.

Defined outcome predictors

Clinical, imaging, and first EEG variables associated with defined outcomes are disclosed in Tables 2–3 and Appendix S3.

First EEG independent predictor of defined outcomes

First EEG background activity asymmetry was an independent predictor of unprovoked seizures during the first year after stroke. The occurrence of interictal epileptiform activity in the first EEG was also an independent predictor of unprovoked seizures. No EEG abnormality independently predicted acute symptomatic seizures. However, the presence of periodic discharges in the first EEG was an independent predictor of epileptiform activity (interictal and/or ictal) in at least one EEG during the hospital stay. No other studied first EEG abnormality was an independent predictor of defined outcomes.

Imaging independent predictor of defined outcomes

ASPECTS was an independent predictor of unprovoked seizures and acute symptomatic seizures. The presence of islands of preserved cortex within the infarct was an independent predictor of the presence of IEA and/or electrographic seizures in at least one EEG during the hospital stay.

Other independent predictors of defined outcomes

Unprovoked seizures were also independently associated with the occurrence of a previous acute symptomatic seizure.

Table 1. EEG abnormalities in different time frames after stroke

	First EEG [a] n (%)	Serial EEG during hospitalization[b] n (%)	McNemar's test 1[c] P	Discharge EEG[d] n (%)	McNemar's test 2[e] P	12M EEG [f] n (%)	McNemar's test 3[g] P
n	151	151	–	143	–	116	–
BA slowing	57 (37.7)	57 (37.7)	ns[h]	32 (22.4)	<0.0005	13 (11.2)	<0.005
BA asymmetry	64 (42.4)	44 (29.1)	<0.0005	42 (29.4)	<0.0005	20 (17.2)	<0.005
Suppression	12 (7.9)	19 (12.6)	0.016	10 (7)	ns	1 (0.9)	ns
NRSA	134 (88.7)	143 (94.7)	0.004	124 (86.7)	ns	99 (85.3)	ns
RSA	26 (17.2)	38 (25.2)	<0.0005	17 (11.9)	ns	9 (7.8)	0.031
LPD	27 (17.9)	38 (25.2)	0.007	9 (6.3)	0.002	3 (2.6)	0.002
IEA	16 (10.6)	18 (11.9)	ns	12 (8.4)	ns	5 (4.3)	ns
EEG Seizures	1 (0.7)	6 (4.0)	ns	0	ns	0	ns

BA, background activity; NRSA, nonrhythmic slow-wave activity; RSA, rhythmic slow-wave activity; LPD, lateralized periodic discharge; IEA, interictal epileptiform activity; EEG Seizures, electrographic seizures.

[a]First EEG - video-EEG (<60 min) performed as early as possible, in the first 72 hours after admission for acute anterior circulation ischemic stroke

[b]Serial EEG during hospitalization - video-EEG (<60 min) performed daily for the first 7 days after stroke (except on weekend), or if neurological worsening unexplained by medical complications and with indication for repeating the imaging exam (at least one EEG record during the hospitalization with one of the analyzed features)

[c]McNemar's test 1 – McNemar's test defining the difference between first EEG and serial EEG during hospitalization

[d]Discharge EEG – video-EEG (<60 min) performed at time of clinical discharge

[e]McNemar's test 2 – McNemar's test defining the difference between first EEG and discharge EEG

[f]12M EEG – video-EEG (<60 min) performed at 12 months after stroke

[g]McNemar's test 3 – McNemar's test defining the difference between first EEG and 12-month EEG

[h]ns - nonsignificant ($p > 0.05$).

Table 2. Clinical, imaging, and neurophysiological predictors of unprovoked seizures (poststroke epilepsy)

Unprovoked seizures	Yes	No	Bivariate analysis[a] *P* OR; 95% CI	Multivariate analysis[b] *P* OR; 95% CI
Demographic and clinical characteristics of patients with >7 days of follow-up (n = 144)				
Number of patients	23	121		
Mean Age (SD)	64.9 (13.3)	67.5 (11.3)	0.466	NA
Median admission NIHSS (IQR)	16 (7)	11 (10)	**0.009**	0.146 1.07; 0.98–1.16
Stroke etiology				
Cardioembolism	14 (60.9%)	62 (51.2%)	0.156	NA
Atherosclerosis	5 (21.7%)	31 (25.6%)		
Small vessels	1 (4.3%)	3 (2.5%)		
Undetermined	1 (4.3%)	23 (19.0%)		
Other	2 (8.7%)	2 (1.7%)		
Previous acute symptomatic seizure	7 (30.4%)	9 (7.4%)	**0.001** **5.44; 1.78–16.65**	**0.019** **4.47; 1.28–15.68**
Imaging stroke characteristics				
Isolated MCA territory infarct patients with >7 days of follow-up (n = 140)				
Number of patients	21	119		
First CT median ASPECTS (IQR)	8 (3)	9 (1)	**0.002**	**0.020** 0.73; 0.56–0.95
First CT median CORTICAL ASPECTS (IQR)	5 (3)	6 (2)	**0.002**	**0.20** 0.73; 0.56–0.95
Isolated MCA infarct patients with a second CT and >7 days of follow-up (n = 119)				
Anterior circulation ischemic stroke patients with a second CT scan and >7 days of follow-up (n = 123)				
Number of patients	23	100		
Islands of preserved cortex within the infarct	8 (34.8%)	17 (17.0%)	0.056 2.60; 0.95–7.11	NA
Hemorrhage	6 (26.1%)	16 (16.0%)	0.255 1.85; 0.63–5.42	NA
First EEG characteristics (n = 151)				
Number of patients	23	121		
BA diffuse slowing	12 (52.2%)	38 (31.4%)	0.055 2.38; 0.96–5.88	NA
BA asymmetry	16 (69.6%)	43 (35.5%)	**0.002** **4.15; 1.58–10.87**	**0.043** 3.16; 1.04–9.65
Suppression	4 (17.4%)	4 (3.3%)	**0.023** **6.16; 1.42–26.74**	NA
NRSAk	22 (95.7%)	106 (87.6%)	0.469 3.11; 0.39–24.81	NA
RWSA	8 (34.8%)	16 (13.2%)	**0.011** **3.50; 1.28–9.58**	0.062 2.92; 0.95–8.97
LPD	7 (30.4%)	18 (14.9%)	0.071 2.50; 0.90–6.94	0.424 1.61; 0.50–5.16
IEA	7 (30.4%)	8 (6.6%)	**0.001** **6.18, 1.97–19.35**	**0.043** 3.84; 1.04–14.13

OR, odds ratio; CI, confidence interval; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale score; IQR, interquartile range; NA, not applicable; MCA, middle cerebral artery; first CT, first CT scan obtain at the emergency department; ASPECTS, Alberta Stroke Program Early CT Score; Cortical ASPECTS – value in ASPECTS considering only the 7 cortical territories of this scale; BA, background activity; NRSA, nonrhythmic slow-wave activity; RSA, rhythmic slow-wave activity; LPD, periodic discharge; IEA, interictal epileptiform activity.

Bold indicates statistical significance ($P < 0.05$).

[a]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by t-test or Mann-Whitney U, as appropriate

[b]Multivariate analysis - variables with a positive significant association in bivariate analysis, were adjusted for age, clinical stroke severity (admission NIHSS) and imaging infarct severity (ASPECTS), using a logistic regression model. The OR for age, NIHSS, and ASPECTS are derived from multivariable logistic models including exclusively these three variables, whereas the OR for the EEG variables are derived from models including age, NIHSS, ASPECTS and the respective EEG variable

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Table 3. Clinical, imaging and neurophysiological predictors of EEG epileptiform activity during hospital stay

IEA and/or EEG seizures during hospital stay	Yes	No	Bivariate analysis[a] p OR; 95% CI	Multivariate analysis[b] p OR; 95% CI
Demographic and clinical characteristics (n = 151)				
Number of patients	27	124		
Mean Age (SD)	70.8 (12.1)	66.6 (12.1)	0.076	NA
Median admission NIHSS (IQR)	15 (15)	12 (10)	**0.019**	0.214 1.05; 0.97–1.13
Stroke etiology				
Cardioembolism	18 (66.7%)	59 (47.6%)	0.388	NA
Atherosclerosis	5 (18.5%)	32 (25.8%)		
Small vessels	0 (0%)	4 (3.2%)		
Undetermined	4 (14.8%)	25 (20.2%)		
Other	0 (0%)	4 (3.2%)		
Imaging stroke characteristics				
Isolated MCA territory infarct (n = 146)				
Number of patients	25	121		
First CT median ASPECTS (IQR)	9 (3)	9 (2)	**0.029**	0.105 0.82; 0.640–1.043
First CT median cortical ASPECTS (IQR)	6 (3)	6 (2)	**0.029**	0.105 0.82; 0.640–1.043
Anterior circulation ischemic stroke patients with a second CT scan (n = 129)				
Number of patients	25	104		
Islands of preserved cortex within the infarct	11 (44.0%)	15 (14.4%)	**0.001** **4.66; 1.78–12.1**	**0.01** **4.29; 1.41–13.1**
Hemorrhage	6 (24.0%)	17 (16.3%)	0.369	NA
First EEG characteristics (n = 151)				
BA diffuse slowing	13 (48.1%)	44 (35.5%)	0.219 1.69; 0.73–3.91	NA
BA asymmetry	18 (66.7%)	46 (37.1%)	**0.005** **3.39; 1.41–8.20**	0.055, 2.64, 0.98–7.14
Suppression	3 (11.1%)	9 (7.3%)	0.450 1.60; 0.40–6.34	NA
NRSA	26 (96.3%)	108 (87.1%)	0.311 3.85; 0.49–30.38	NA
RWSA	7 (25.9%)	19 (15.3%)	0.186 1.93; 0.72–5.20	NA
LPD	12 (44.4%)	15 (12.1%)	**<0.0005** **5.81; 2.29–14.76**	**0.009** **3.88, 1.41–10.70**
IEA	16 (59.3%)	0 (0%)	**NA**	NA

OR, odds ratio; CI, confidence interval; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale score; IQR, Interquartile range; NA, not applicable; MCA, middle cerebral artery; first CT, first CT scan obtain at the emergency department; ASPECTS, Alberta Stroke Program Early CT Score; Cortical ASPECTS, Score in ASPECTS considering only the 7 cortical territories of this scale; BA, background activity; NRSA, nonrhythmic slow wave activity; RSA, rhythmic slow wave activity; LPD, lateralized periodic discharge; IEA, interictal epileptiform activity.

Bold indicates statistical significance ($P < 0.05$).

[a]Bivariate analysis - bivariate analysis of dichotomous data performed by chi-square test or Fisher's exact test and quantitative variables by *t*-test or Mann-Whitney test, as appropriate.

[b]Multivariate analysis - variables with a positive significant association in bivariate analysis, were adjusted for age, clinical stroke severity (admission NIHSS), and imaging infarct severity (ASPECTS), using a logistic regression model. The ORs for age, NIHSS, and ASPECTS are derived from multivariable logistic models including exclusively these 3 variables, whereas the ORs for the EEG variables are derived from models including age, NIHSS, ASPECTS, and the respective EEG variable. Bold values – $p < 0.05$

Table 4 displays the characteristics of prediction models for defined outcomes. All models have a good to very good discriminative capacity.

Discussion

In this work, poststroke epilepsy could be predicted by EEG findings, extracted from visual analysis of an early and short-duration EEG, independently from clinical and imaging-based infarct severity. Indeed, for the same age and clinical and imaging infarct severity, the risk of poststroke unprovoked seizures was 3.2 times higher in patients with first EEG background activity asymmetry and 3.8 times higher if interictal epileptiform activity was displayed in this recording. Furthermore, we found early neurophysiological markers of an increased risk of EEG epileptiform activity during the hospital stay, thereby identifying patients who might benefit from an extended neurophysiological

Table 4. Defined outcomes binary logistic regression models characteristics

Model features	Omnibus test	Nagelkerke's R^2	Hosmer-Lemeshow test	PAC	SEN	SPE	PPV	NPV	AUC 95%CI
Post-stroke unprovoked seizures (post-stroke epilepsy)									
Independent variables: "previous post-stroke acute symptomatic seizures" + "1st CT ASPECTS" + 1st EEG background activity asymmetry + 1st EEG with interictal epileptiform activity									
Model characteristics	$\chi^2(4) = 22.58$ $p < 0.0005$	26,1%	$\chi^2(6) = 5.11$, $p = 0.53$	85.7%	23.8%	96.6%	55.6%	87.8%	0.81 0.71–0.90
Poststroke acute symptomatic seizures									
Independent variables: "1st CT ASPECTS"									
Model characteristics	$\chi^2(1) = 6.50$ $p = 0.013$	7.9%	$\chi^2(3) = 0.23$, $p = 0.830$	86.3%	0%	100%	0%	100%	0.72 0.63–0.82
EEG epileptiform (interictal and/or ictal) activity during hospital stay									
Independent variables: "Islands of preserved cortex within the infarct" + "1st EEG with periodic discharges"									
Model characteristics	$\chi^2(2) = 19.49$ $p < 0.0005$	22.4%	$\chi^2(2) = 0.993$, $p = 0.609$	84.5%	28.0%	98.1%	77.8%	85.0%	0.72 0.60–0.85

PAC, percentage of accuracy in classification; SEN, Sensibility; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the ROC (receiver-operating characteristic) curve; CI, confidence interval; ASPECTS, Alberta Stroke Program Early CT Score.

study. A previous analysis of our group[11] already showed that the frequency of poststroke seizures is clinically underestimated without a systematic neurophysiological evaluation. The present study further enlarges the importance of EEG in stroke patients, defining the characteristics of those with an increased for epilepsy and also for paroxysmal EEG events during the hospital stay.

Strengths of this work include the sample size, with prospective clinical assessment and rigorous electroencephalographic acute evaluation and follow-up. Furthermore, this work includes standardized imaging evaluation of MCA infarct dimension and the presence of islands of preserved cortex within the infarct. Another aspect that stands out is the use of internationally recognized terminology,[19] showing good interobserver agreement,[27] for describing the electroencephalographic features. The consideration of clinical and imaging parameters in the statistic models is also pertinent.

In this study, the noncontinuous nature of the neurophysiological assessment may be considered a limitation. However, we identified early neurophysiological and imaging markers that can guide the need for a more prolonged study (serial or even continuous) only in some patients, presumably improving the cost-benefit of such a procedure. Continuous EEG requires large quantities of time, specialized human resources (physicians and technicians), and is not accessible at all centers. Accordingly, studies about the performance of a short duration EEG for epileptiform activity detection are important. In fact, the search for EEG markers suggesting the need and helping to identify patients for a more prolonged or frequent record, as analyzed in this paper, is a current trend in EEG research.[28–31] Furthermore, antiepileptic drug prescription was not analyzed in this study. Although (theoretically) antiepileptic drug treatment could affect outcomes, primary and secondary prophylaxis of an index acute symptomatic seizure is not routinely performed in our stroke unit, in accordance with the recently published ESO guidelines.[32] Furthermore, even when repeated acute symptomatic seizures occur during a hospital stay leading to antiepileptic drug prescription, their withdrawal after the acute stroke phase is encouraged. Therefore, the occurrence of unprovoked seizures 1 year after stroke is probably not greatly affected by antiepileptic drug prescription in our study.

In the present work, unprovoked seizures or epilepsy (according to the current International League Against Epilepsy [ILAE] definition[5]) in the year following an anterior circulation ischemic stroke was independently predicted by first EEG asymmetry (reflecting asymmetrical cerebral dysfunction) even when adjusted for age, admission NIHSS score, and ASPECTS. These data add a neurophysiological risk factor to poststroke seizures, reflecting not only their association with large and disabling ischemic strokes[33] but also the importance of EEG for brain functional assessment. In fact, recently, first EEG asymmetry was also reported as an independent predictor of unfavorable stroke functional outcome, even when adjusted for age and clinical and imaging stroke severity.[34]

Furthermore, poststroke epilepsy was also independently predicted by the presence of IEA in the first EEG. This observation seems physiopathologically coherent, because spikes and sharp waves are neurophysiological markers of epileptogenesis[35] and therefore of an increased susceptibility for seizures. This result is also of great clinical relevance, helping to identify patients with an increased risk for poststroke epilepsy.

There is currently no high-quality evidence providing strong support for the primary prophylactic use of antiepileptic drugs for postischemic stroke unprovoked seizures.[32] However, we think that our EEG findings can, at least, support more strict clinical monitoring, oriented toward an early recognition of seizures in these higher risk patients, and may help earlier identification, prevention of associated risks, and timely prescription of appropriate

secondary prophylaxis of poststroke unprovoked seizures. On the other hand, one should note that the European Stroke Organization's "weak recommendation" against primary prophylaxis of unprovoked seizures is based on their low risk of occurrence in most stroke patients (approximately 10%).[32] Although lacking external validation, our model might help to consider the need for antiepileptic drugs when EEG and other independent predictors of poststroke epilepsy are present, that is, whenever the estimated risk of an unprovoked seizure occurrence is at least similar to its recurrence risk[32]: >60% (95% CI 59.7–81.9%).[17]

In our study, first EEG periodic discharges were an independent predictor of epileptiform activity (interictal and/or ictal) during hospital stay, reinforcing the notion that periodic discharges are in the continuum between an interictal and ictal phenomenon[36] and in accordance with the association of this neurophysiological feature to clinical and EEG epileptiform manifestations both in studies using the short duration[4,14,37] and continuous EEG.[28,29,38] Another independent predictor of epileptiform activity in our study was the presence of islands of preserved cortex within the infarct. Although suggested by 2 case-control studies from the 1990s,[14,15] this association has not yet been prospectively associated with EEG epileptiform activity during hospital stay for acute stroke. It has been postulated that this finding reflects regional cerebral blood flow reduction, although at a threshold higher than that of ischemia,[15] providing a state of neuronal hyperexcitability to these regions. Periinfarct depolarizations have been observed in stroke animal models[39] and positron emission tomography (PET) studies have shown that most patients with unprovoked seizures have hypermetabolism in the infarct boundaries.[40] In addition, a recent study[41] demonstrated that IEA is associated with several separated cortical microinjuries, postulating that its presence may interrupt the connectivity between cortical deep and superficial layers and induce hypersynchronization of the latter ones.

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Disclosure of Conflict of Interests

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References

1. Pitkänen A, Roivainen R, Lukasiuk K. Development of epilepsy after ischaemic stroke. *Lancet Neurol* 2015;15:185–197.
2. Jordan K. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. *J Clin Neurophysiol* 2004;21:341–352.
3. Assenza G, Di Lazzaro V. A useful electroencephalography (EEG) marker of brain plasticity: delta waves. *Neural Regen Res* 2015;10:1216–1217.
4. De Reuck J, Goethals M, Claeys I, et al. EEG findings after a cerebral territorial infarct in patients who develop early- and late-onset seizures. *Eur Neurol* 2006;55:209–213.
5. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* 2014;55:475–482.
6. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521–1526.
7. Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: Implications for stroke clinical trials - A literature review and synthesis. *Stroke* 2007;38:1091–1096.
8. ESO. Guidelines for management of ischaemic stroke and transient Ischaemic Attack 2008. *Cerebrovasc Dis* 2008;25:457–507.
9. Adams H, Bendixen B, Kappelle L, et al. Classification of subtype of acute ischemic stroke. *Stroke* 1993;23:35–41.
10. Ottman R, Barker-Cummings C, Leibson CL, et al. Validation of a brief screening instrument for the ascertainment of epilepsy. *Epilepsia* 2010;51:191–197.
11. Bentes C, Martins H, Peralta AR, et al. Post-stroke seizures are clinically underestimated. *J Neurol* 2017;264:1978–1985.
12. Barber P, Demchuk A, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000;355:1670–1674.
13. Anon. The SITS Monitoring Study (SITS-MOST) Final Protocol, 2002. Available at:http://www.acutestroke.org/SM_Protocol/SITS-MOST_final_protocol.pdf. Accessed February 20, 2018.
14. Ryglewicz D, Baranska-Gieruszczak M, Niedzielska K, et al. EEG and CT findings in poststroke epilepsy. *Acta Neurol Scand* 2013;81:488–490.
15. Awada A, Omojola MF, Obeid T. Late epileptic seizures after cerebral infarction. *Acta Neurol Scand* 1999;99:265–268.
16. Pohlmann-Eden B, Fatar M, Hennerici M. The preserved cortical island sign is highly predictive of postischemic seizures. *Cerebrovasc Dis* 2001;12:282.
17. Hesdorffer DC, Benn EKT, Cascino GD, et al. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia* 2009;50:1102–1108.
18. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 2010;51:671–675.
19. Hirsch LJ, LaRoche SM, Gaspard N, et al. American clinical neurophysiology society's standardized critical care EEG terminology: 2012 VERSION. *J Clin Neurophysiol* 2013;30:1–27.
20. Noachtar S, Binnie C, Ebersole J, et al. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999;52:21–41.
21. Goldstein L, Bertels C, Davis J. Interrater reliability of the NIH stroke scale. *Arch Neurol* 1989;46:660–662.
22. Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. *Epilepsia* 2013;54:28–29.
23. Adams HPJ, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999;53:126–131.

24. Knoflach M, Matosevic B, Rucker M, et al. Functional recovery after ischemic stroke - A matter of age. *Neurology* 2012;78:279.
25. Vogt G, Laage R, Shuaib A, et al. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: An analysis of the Virtual International Stroke Trials Archive (VISTA) database. *Stroke* 2012;43:1266–1272.
26. Bentes C, Martins H, Peralta AR, et al. Epileptic manifestations in stroke patients treated with intravenous alteplase. *Eur J Neurol* 2017;24:755–761.
27. Gaspard N, Hirsch LJ, LaRoche SM, et al. Interrater agreement for Critical Care EEG Terminology. *Epilepsia* 2014;55:1366–1373.
28. Swisher CB, Shah D, Sinha SR, et al. Baseline EEG pattern on continuous ICU EEG monitoring and incidence of seizures. *J Clin Neurophysiol* 2015;32:147–151.
29. Westover MB, Shafi MM, Bianchi MT, et al. The probability of seizures during EEG monitoring in critically ill adults. *Clin Neurophysiol* 2015;126:463–471.
30. Koren J, Herta J, Draschtak S, et al. Prediction of rhythmic and periodic EEG patterns and seizures on continuous EEG with early epileptiform discharges. *Epilepsy Behav* 2015;49:286–289.
31. Shafi MM, Westover MB, Cole AJ, et al. Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG. *Neurology* 2012;79:1796–1801.
32. Holtkamp M, Beghi E, Benninger F, et al. European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy. *Eur Stroke J* 2017;2:103–115.
33. Ferro J, Bentes C. Post-Stroke Epilepsy. *Aging Health* 2006;2:599–609.
34. Bentes C, Peralta AR, Martins H, et al. Seizures, electroencephalographic abnormalities, and outcome of ischemic stroke patients. *Epilepsia Open* 2017;2:441–452.
35. Engel J, Pitkanen A, Loeb JA, et al. Epilepsy biomarkers. *Epilepsia* 2013;54:61–69.
36. Chong D, Hirsch L. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. *J Clin Neurophysiol* 2005;22:79–91.
37. Mecarelli O, Pro S, Randi F, et al. EEG patterns and epileptic seizures in acute phase stroke. *Cerebrovasc Dis* 2011;31:191–198.
38. Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 2004;62:1743–1748.
39. Iijima T, Mies G, Hossmann K. Repeated negative DC deflections in rat cortex following middle cerebral artery occlusion are abolished by MK-801 : effect on volume of ischemic injury repeated negative DC deflections in rat cortex abolished by MK-801 : Effect on Volume of. *J Cereb Blood Flow Metab* 1992; 12:727–733.
40. De Reuck J, Vonck K, Santens P, et al. Cobalt-55 positron emission tomography in late-onset epileptic seizures after thrombo-embolic middle cerebral artery infarction. *J Neurol Sci* 2000;181:13–18.
41. Dachet F, Bagla S, Keren-Aviram G, et al. Predicting novel histopathological microlesions in human epileptic brain through transcriptional clustering. *Brain* 2015;138:356–370.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Clinical and imaging characteristics and first EEG abnormalities.

Appendix S2. Clinical imaging characteristics and first EEG abnormalities in patients with (vs without) EEG seizures during hospital stay.

Appendix S3. Clinical imaging and neurophysiological predictors of acute symptomatic seizures.

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FULL-LENGTH ORIGINAL RESEARCH

Seizures, electroencephalographic abnormalities, and outcome of ischemic stroke patients

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Summary

Objective: Seizures and electroencephalographic (EEG) abnormalities have been associated with unfavorable stroke functional outcome. However, this association may depend on clinical and imaging stroke severity. We set out to analyze whether epileptic seizures and early EEG abnormalities are predictors of stroke outcome after adjustment for age and clinical/imaging infarct severity.

Methods: A prospective study was made on consecutive and previously independent acute stroke patients with a National Institutes of Health Stroke Scale (NIHSS) score ≥ 4 on admission and an acute anterior circulation ischemic lesion on brain imaging. All patients underwent standardized clinical and diagnostic assessment during admission and after discharge, and were followed for 12 months. Video-EEG (<60 min) was performed in the first 72 h. The Alberta Stroke Program Early CT Score quantified middle cerebral artery infarct size. The outcomes in this study were an unfavorable functional outcome (modified Rankin Scale [mRS] ≥ 3) and death (mRS = 6) at discharge and 12 months after stroke.

Results: Unfavorable outcome at discharge was independently associated with NIHSS score ($p = 0.001$), EEG background activity slowing ($p < 0.001$), and asymmetry ($p < 0.001$). Unfavorable outcome 1 year after stroke was independently associated with age ($p = 0.001$), NIHSS score ($p < 0.001$), remote symptomatic seizures ($p = 0.046$), EEG background activity slowing ($p < 0.001$), and asymmetry ($p < 0.001$). Death in the first year after stroke was independently associated with age ($p = 0.028$), NIHSS score ($p = 0.001$), acute symptomatic seizures ($p = 0.015$), and EEG suppression ($p = 0.019$).

Significance: Acute symptomatic seizures were independent predictors of vital outcome and remote symptomatic seizures of functional outcome in the first year after stroke. Therefore, their recognition and prevention strategies may be clinically relevant. Early EEG abnormalities were independent predictors and comparable to age and early clinical/imaging infarct severity in stroke functional outcome discrimination, reflecting the concept that EEG is a sensitive and robust method in the functional assessment of the brain.

KEY WORDS: Seizures, Epilepsy, EEG, Stroke, Outcome, Alberta Stroke Program Early CT Score.

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Key Points

- Remote symptomatic seizures were independent predictors of unfavorable outcome 1 year after stroke
- Acute symptomatic seizures were independent predictors of vital outcome in the first year after stroke
- Early poststroke raw EEG abnormalities were independent predictors of stroke functional outcome at discharge and 1 year after stroke
- Early poststroke raw EEG abnormalities were independent predictors of stroke vital outcome 1 year after stroke
- Early poststroke EEG asymmetry had the highest odds of impacting stroke functional outcome at discharge and 12 months after stroke

Poststroke epileptic phenomena (seizures and status epilepticus)[1–6] have been associated with ischemic stroke unfavorable outcome. However, although electroencephalography (EEG) is essential for the detection of interictal and ictal epileptiform activity, it is unknown whether these EEG activities per se are also associated with stroke prognosis.

Previous work, mainly retrospective and without standardized imaging analysis, showed that raw EEG abnormalities (other than epileptiform discharges) are associated with poststroke functional outcome, essentially in the short term.[7–11] Additionally, a few small sample studies using quantitative EEG indexes showed that these might be better than a clinical scale in functional outcome prediction[12] or have a higher correlation with the residual neurological deficit after stroke than acute magnetic resonance imaging (MRI) lesion.[13]

However, it is unknown whether the association between seizures or EEG abnormalities and stroke functional outcome is independent from known cerebral infarct outcome predictors, namely age and stroke (clinical and imaging) severity.[14–17] Thus, we aimed to prospectively assess whether seizures and poststroke EEG abnormalities are outcome predictors at discharge and 12 months after stroke after adjustment for age and stroke severity.

Methods

Study design

We performed a prospective longitudinal study of consecutive anterior circulation ischemic stroke patients admitted to the stroke unit of the neurology department of a university hospital over a period of 24 months and followed for 12 months. The ethics committee "Comissão de Ética para a Saúde" at our hospital approved this study. All subjects or their next of kin gave written informed consent for participation.

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All included patients had to be previously independent (modified Rankin Scale [mRS] ≤ 1), score a value of at least 4 on the National Institutes of Health Stroke Scale (NIHSS)[18] upon admission to the emergency department, and have an acute ischemic brain lesion (noncontrast computed tomography [CT] scan or MRI) in the internal carotid artery territory and no previous history of epileptic seizures, traumatic head injury requiring hospital admission, or brain surgery.

Clinical assessment

All patients received standardized clinical and diagnostic assessment, during admission and after discharge. An investigator blinded to the neurophysiological evaluation conducted a phone interview at 6 months and a clinical appointment 12 months after stroke to access the occurrence of epileptic seizures and functional outcome.

NIHSS score at admission assessed clinical stroke severity. The functional outcome at discharge and at 12 months was assessed by the mRS.[19]

Neurophysiological evaluation

Patients underwent a neurophysiological evaluation protocol that included a 64-channel video-EEG with a maximum duration of 60 min in the first 72 h after stroke (EEG). The record included an eyes closed wake resting condition and eyes open, hyperventilation, and photic stimulation maneuvers. EEG review and classification were performed by a certified clinical neurophysiologist (C.B.) using international criteria and terminology,[20–22] blinded to clinical and imaging findings. All doubts were decided by consensus with another clinical neurophysiologist (A.R.P.).

Neuroimaging interpretation

A senior neuroradiologist (C.M. or C.C.) blinded for clinical and EEG findings analyzed all the neuroimaging studies performed during hospitalization. Doubts were decided by consensus. In patients with an isolated middle cerebral artery (MCA) stroke in the imaging study (by noncontrast-enhanced CT scan or MRI), the infarct size was quantified in the first CT performed after stroke by the Alberta Stroke Program Early CT Score (ASPECTS).[17] Whenever there was a brain CT scan performed at least 24 h after stroke onset (second CT scan), ASPECTS was also quantified in this examination in patients with an isolated MCA infarct.

Predictors and outcomes

The following predictors were registered:

1. Clinical predictors: age, gender, TOAST (Trial of Org 10172 in Acute Stroke Treatment) subgroups,[23] NIHSS on admission, occurrence of poststroke seizures[24–26] (either acute symptomatic [in the first 7 days after stroke[25]] or remote symptomatic [after that time point[26]]), and status epilepticus.[22,27,28]

2. Neuroimaging predictors: ASPECTS in the first and second CT scans and any type of hemorrhage transformation[29] in the second CT scan.
3. EEG predictors (categorical variables, dichotomized into present or absent): background activity slowing[20]; asymmetry[21]; suppression (focal, hemispheric, or diffuse)[21]; focal slow wave activity (including focal and regional concept)[20]; rhythmic slow wave activity, including rhythmic delta activity according to the definition of the American Clinical Neurophysiology Society[21] and rhythmic delta/theta (>0.5 Hz)[22]; interictal epileptiform activity[20]; and periodic discharges.[21]

The outcomes in this study were an unfavorable functional outcome (mRS ≥ 3) and death (mRS = 6) at discharge and 12 months after stroke.

Statistical analysis

A descriptive analysis was used for nominal qualitative and quantitative variables (discrete and continuous). Nominal variables are expressed in frequency, discrete variables as medians and interquartile ranges, and continuous variables as means and standard deviations (SDs).

Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate. Variables with a significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke,[14–17] namely age, clinical stroke severity (admission NIHSS), and imaging infarct size (ASPECTS), using a logistic regression model. The significance level was $\alpha \leq 0.05$. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Outcome prediction model characteristics encompassing poststroke seizures or EEG abnormalities with the highest odds of impacting outcome were compared with the model including exclusively known stroke outcome predictors. The percentage of patients correctly identified by the models was calculated. Model calibration was analyzed by Hosmer–Lemeshow test, and its discriminative capacity was measured by the area under the receiver operating characteristic (ROC) curve (95% CI).

Statistical analysis was done using the SPSS program (version 24 for Mac).

Results

One hundred fifty-one patients (112 men and 39 women) were included, with a mean age of 67.4 (SD = 11.9) years. During this study, 23 patients died (seven during admission before day 7, 11 between discharge and 6 months after stroke, and five after that time point). One patient (0.66%) was lost for clinical and EEG follow-up in the last 6 months of the study. From the 127 living patients with a clinical follow-up 1 year after stroke, 117 (92.1%) had repeated EEG by that time. The study flowchart was previously described.[30] All (151) patients had at least one acute CT scan (first CT). Furthermore, in the acute phase, a second CT scan was performed in 129 (85.4%) patients and an MRI in 63 (41.7%) patients. From the 129 patients who received a second CT scan, only 124 had an isolated MCA infarct.

Variables associated with stroke outcome at discharge

Table 1 describes clinical, imaging, and neurophysiological features of included patients, comparing unfavorable outcome (mRS ≥ 3) patients with those with a favorable outcome (mRS < 3) at discharge. In bivariate analysis, an unfavorable outcome was more frequent in older patients, and patients with a higher admission NIHSS, a lower ASPECTS, presence of hemorrhagic transformation, and an EEG with background activity slowing, asymmetry, focal slow wave activity, and periodic discharges. After adjustment of these variables for known functional outcome predictors of stroke, admission NIHSS, EEG background activity slowing, asymmetry, and periodic discharges predicted functional outcome. Second (but not first) CT ASPECTS was a discharge outcome predictor independent from age and NIHSS.

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG background activity asymmetry (Table 2), the variables remaining independent predictors were NIHSS score (OR = 1.16, 95% CI = 1.07–1.27, p = 0.001) and background activity asymmetry (OR = 11.90, 95% CI = 3.73–38.46, p < 0.001). This model correctly classified 76.7% of the subjects, and the area under the ROC curve was 0.86. The prediction model including this EEG variable did not have a different discriminative capacity compared to the model encompassing the already known outcome predictors.

Clinical, imaging, and neurophysiological features of patients who died during hospitalization can be seen in Table 3. In bivariate analysis, an association was found with admission NIHSS, occurrence of acute symptomatic seizures, and EEG background activity slowing and suppression. Adjustment for known functional outcome predictors of stroke was not performed due to the low number of events (n = 7).

Variables associated with stroke outcome at 12 months

Table 4 describes clinical, imaging, and neurophysiological features of included patients, comparing those with unfavorable (mRS ≥ 3) and favorable outcome (mRS < 3). An association with unfavorable outcome was found in bivariate analysis for age, admission NIHSS, treatment with intravenous alteplase, occurrence of an acute or remote symptomatic seizure, ASPECTS, and EEG background activity slowing, asymmetry, suppression, focal and rhythmic slow wave activity, periodic discharges, and interictal epileptiform activity. After adjustment for known functional outcome predictors of stroke age, admission NIHSS, occurrence of a remote symptomatic seizure, and EEG

Table 1. Clinical, imaging, and neurophysiological features and discharge functional outcome of anterior circulation ischemic stroke patients

At discharge	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
Clinical features, n = 151	52	99		
Male	29 (55.8%)	60 (60.4%)	p = 0.566	NA
Mean age, yr (SD)	64.48 (13.20)	68.86 (10.97)	**p = 0.032**	OR = 1.02, 95% CI = 0.99–1.06, p = 0.246
Median admission NIHSS (IQR)	8 (6)	15 (10)	**p < 0.001**	OR = 1.18, 95% CI = 1.10–1.28, **p < 0.001**
IV alteplase	31 (59.6%)	70 (70.7%)	p = 0.169	NA
Stroke etiology				
Cardioembolism	21 (40.4%)	56 (56.6%)	NA	NA
Atherosclerosis	16 (30.8%)	21 (21.2%)		
Small vessels	2 (3.8%)	2 (2.0%)		
Unknown	13 (25.0%)	16 (16.2%)		
Other	0 (0%)	4 (4.0%)		
Acute symptomatic seizures	4 (7.7%)	18 (18.2%)	p = 0.094	NA
Nonconvulsive status epilepticus	0 (0%)	4 (4%)	p = 0.229	NA
Isolated MCA territory infarct patients with a first CT, n = 146	50	96		
Median ASPECTS (IQR)	10 (1)	9 (3)	**p = 0.042**	OR = 0.84, 95% CI = 0.63–1.10, p = 0.203
Isolated MCA territory infarct patients with a second CT, n = 124	35	89		
Median ASPECTS (IQR)	8 (2)	5 (4)	**p < 0.001**	OR = 0.61, 95% CI = 0.47–0.80, p < 0.001
Anterior circulation ischemic stroke patients with a second CT, n = 129	37	92		
Hemorrhagic transformation	2 (5.4%)	21 (22.8%)	**p = 0.021**	OR = 3.02, 95% CI = 0.62–14.73, p = 0.171
First EEG findings, n = 151	52	99		
Background activity slowing	6 (11.5%)	51 (51.5%)	**p < 0.001**	OR = 5.55, 95% CI = 1.89–16.33, **p = 0.002**
Background activity asymmetry	4 (7.7%)	60 (60.6%)	**p < 0.001**	OR = 11.91, 95% CI = 3.73–38.46, **p < 0.001**
EEG suppression	1 (1.9%)	11 (11.1%)	p = 0.059	NA
FSWA	42 (80.8%)	92 (92.9%)	**p = 0.025**	OR = 1.24, 95% CI = 0.36–4.24, p = 0.736
RSWA	5 (9.6%)	21 (21.2%)	p = 0.073	NA

Continued

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Table 1. Continued.

At discharge	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
Periodic discharges	1 (1.9%)	26 (26.3%)	**p < 0.001**	OR = 10.39, 95% CI = 1.30–83.03, **p = 0.027**
IEA	2 (3.8%)	14 (14.1%)	p = 0.056	NA

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; EEG, electroencephalographic; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RSWA, rhythmic slow wave activity; SD, standard deviation.

[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.

[b]Variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS), and imaging infarct severity (ASPECTS), using a logistic regression model. First CT ASPECTS was used except in the model including second CT ASPECTS. The ORs for NIHSS, age, and ASPECTS are derived from multivariate logistic models including exclusively these three variables, whereas the ORs for the EEG variables are derived from models including NIHSS, age, ASPECTS, and the respective EEG variable.

Bold values indicate $p \leq 0.05$.

Table 2. Comparison between stroke outcome (mRS ≥ 3) prediction model characteristics at discharge

Logistic regression models for an unfavorable outcome (mRS ≥ 3) at discharge

Model features	Omnibus test[a]	Nagelkerke R^2[b]	Hosmer–Lemeshow test[c]	PAC	SEN	SPE	PPV	NPV	AUC, 95%CI
Independent variables included in the model									
KP[d]	$\chi^2(3) = 34.85$, $p < 0.001$	29.4%	$\chi^2(8) = 4.86$, $p = 0.773$	73.3%	85.4%	50.0%	76.6%	64.1%	0.78, 0.70–0.86
EEG[e]	$\chi^2(1) = 44.86$, $p < 0.001$	35.5%	$\chi^2(0) = 0.00$, —	71.5%	60.6%	92.3%	93.8%	55.2%	0.76, 0.69–0.84
KP[d] + EEG[e]	$\chi^2(4) = 59.25$, $p < 0.001$	46.1%	$\chi^2(8) = 3.67$, $p = 0.885$	76.7%	81.3%	68.0%	83.0%	65.4%	0.86, 0.79–0.92

AUC, area under receiving operator curve; CI, confidence interval; EEG, electroencephalography; KP, known predictors; mRS, modified Rankin Scale; NPV, negative predictive value; PAC, percentage accuracy in classification (% of cases correctly classified by the model); PPV, positive predictive value; SEN, sensitivity; SPE, specificity.

[a]Omnibus test of model coefficients provides the overall statistical significance of the model, that is, how well the model predicts outcome to no independent variables.

[b]Nagelkerke R^2 is a method of calculating the explained variation, that is, how much variation of the outcome can be explained by the model.

[c]Hosmer–Lemeshow goodness of fit test analyzes how poor the model is at predicting outcome. When not significant, it indicates that the model is not a poor fit.

[d]Known stroke outcome predictors: age, admission National Institutes of Health Stroke Scale, and Alberta Stroke Program Early CT Score.

[e]EEG background activity asymmetry (EEG variable with the highest odds of impacting outcome; please refer to Table 1).

background activity slowing, asymmetry, and periodic discharges remained significant. Second (but not first) CT ASPECTS was a discharge outcome predictor independent from age and NIHSS.

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG asymmetry (Table 5A), the variables remaining independent predictors were age (OR = 1.09, 95% CI = 1.09–1.04, p = 0.001), NIHSS score (OR = 1.18, 95% CI = 1.07–1.29, p = 0.001), and EEG background activity asymmetry (OR = 22.73, 95% CI = 7.30–71.43, p < 0.001). This model correctly classified 84.8% of the subjects, and the area under the ROC curve was 0.91. The prediction model including this EEG variable did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

In the logistic regression model encompassing known functional outcome predictors of stroke and remote symptomatic seizures (Table 5A), the variables remaining independent predictors were age (OR = 1.08, 95% CI = 1.04–1.14, p < 0.001), NIHSS score (OR = 1.18, 95% CI = 1.09–1.28, p < 0.001), and remote symptomatic seizures (OR = 3.76, 95% CI = 1.02–13.83, p = 0.046). This model correctly classified 74.8% of the subjects, and the area under the ROC curve was 0.83. The prediction model including this type of poststroke seizure did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

Clinical, imaging, and neurophysiological features of patients who died in the first year after stroke are disclosed in Table 6. An association with death in the first year after stroke was found in bivariate analysis for age, admission NIHSS, occurrence of an acute symptomatic seizure, and EEG background activity slowing, asymmetry, suppression, and periodic discharges. After adjustment for known functional outcome predictors of stroke age, admission NIHSS, occurrence of an acute symptomatic seizure, and EEG suppression remained significant.

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG suppression (Table 5B), the variables remaining independent predictors were age (OR = 1.06, 95% CI = 1.01–1.12, p = 0.032), NIHSS score (OR = 1.18, 95% CI = 1.07–1.31,

Table 3. Clinical, imaging, and neurophysiological features and vital outcome of anterior circulation ischemic stroke patients at discharge

At discharge	Death	Alive	Bivariate analysis[a]
Clinical features, n = 151	7	144	
Male	5 (71.4%)	84 (58.3%)	p = 0.701
Mean age, yr (SD)	71.14 (8.80)	67.17 (12.06)	p = 0.391
Median admission NIHSS (IQR)	20 (9)	12 (10)	**p = 0.032**
IV alteplase	5 (71.4%)	96 (66.7%)	p = 1.000
Stroke etiology			
Cardioembolism	1 (14.3%)	76 (52.8%)	NA
Atherosclerosis	1 (14.3%)	36 (25.0%)	
Small vessels	0 (0%)	4 (2.8%)	
Unknown	5 (71.4%)	24 (16.7%)	
Other	0 (0%)	4 (2.8%)	
Acute symptomatic seizures	6 (85.7%)	16 (11.1%)	**p < 0.001**
Nonconvulsive status epilepticus	1 (14.3%)	3 (2.1%)	p = 0.175
Isolated MCA territory infarct patients with a first CT, n = 146	6	140	
Median ASPECTS (IQR)	8.5 (5)	9 (2)	p = 0.343
Isolated MCA territory infarct patients with a second CT, n = 124	5	119	
Median ASPECTS (IQR)	3 (7)	6 (4)	p = 0.125
Anterior circulation ischemic stroke patients with a second CT, n = 129	6	123	
Hemorrhagic transformation	1 (16.7%)	22 (17.9%)	p = 1.000
First EEG findings, n = 151	7	144	
Background activity slowing	7 (100%)	50 (34.7%)	**p = 0.001**
Background activity asymmetry	5 (71.4%)	59 (41.0%)	p = 0.135
EEG suppression	4 (57.1%)	8 (5.6%)	**p = 0.001**
FSWA	6 (85.7%)	128 (88.9%)	p = 0.574
RSWA	2 (28.6%)	24 (16.7%)	p = 0.346
Periodic discharges	2 (28.6%)	25 (17.4%)	p = 0.609
IEA	1 (14.3%)	15 (10.4%)	p = 0.551

ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; EEG, electroencephalographic; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; RSWA, rhythmic slow wave activity; SD, standard deviation.

[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.

Bold values indicate p ≤ 0.05.

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Table 4. Clinical, imaging, and neurophysiological features and functional outcome at 12 months after anterior circulation ischemic stroke

At 12 months after stroke	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
Clinical features, n = 150	73	77		
Male	40 (54.8%)	48 (62.3%)	p = 0.348	NA
Mean age, yr (SD)	63.45 (12.19)	71.23 (10.37)	**p < 0.001**	OR = 1.07, 95% CI = 1.03–1.12, **p = 0.001**
Median admission NIHSS (IQR)	9 (8)	17 (9)	**p < 0.001**	OR = 1.18, 95% CI = 1.1–1.28, **p < 0.001**
IV alteplase	43 (58.9%)	58 (75.3%)	**p = 0.032**	OR = 1.41, 95% CI = 0.59–3.74, p = 0.407
Stroke etiology				
Cardioembolism	34 (46.6%)	43 (55.8%)	NA	NA
Atherosclerosis	18 (24.7%)	18 (23.4%)		
Small vessels	3 (4.1%)	1 (1.3%)		
Unknown	16 (21.9%)	13 (16.9%)		
Other	2 (2.7%)	2 (2.6%)		
Acute symptomatic seizures	5 (6.8%)	17 (22.1%)	**p = 0.008**	OR = 2.19, 95% CI = 0.63–7.66, p = 0.220
Nonconvulsive status epilepticus	0 (0%)	4 (5.2%)	p = 0.121	NA
Remote symptomatic seizures	5 (6.8%)	18 (25.7%)	**p = 0.002**	OR = 3.76, 95% CI = 1.02–13.83, **p = 0.046**
Seizures anytime during the study	9 (12.3%)	29 (37.7%)	**p < 0.001**	OR = 2.19, 95% CI = 0.80–6.04, p = 0.128
Isolated MCA territory infarct patients with a first CT, n = 145	71	74		
Median ASPECTS (IQR)	10 (1)	9 (3)	**p = 0.029**	OR = 0.90, 95% CI = 0.61–1.04, p = 0.089
Isolated MCA territory infarct patients with a second CT, n = 124	54	70		
Median ASPECTS (IQR)	8 (3)	4.5 (5)	**p < 0.001**	OR = 0.68, 95% CI = 0.54–0.84, p = 0.001
Anterior circulation ischemic stroke patients with a second CT, n = 129	56	73		
Hemorrhagic transformation	7 (12.5%)	16 (21.9%)	p = 0.166	NA
First EEG findings, n = 150	73	77		
Background activity slowing	7 (9.6%)	50 (64.9%)	**p < 0.001**	OR = 14.50, 95% CI = 4.95–42.48, **p < 0.001**
Background activity asymmetry	8 (11.0%)	56 (72.7%)	**p < 0.001**	OR = 22.73, 95% CI = 7.30–71.43, **p < 0.001**

Continued

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Table 4. Continued.

At 12 months after stroke	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
EEG suppression	1 (1.4%)	10 (13.0%)	**p = 0.009**	OR = 8.85, 95% CI = 0.71–110.22, p = 0.09
FSWA	60 (82.2%)	73 (94.8%)	**p = 0.020**	OR = 1.60, 95% CI = 0.36–7.02, p = 0.534
RSWA	8 (11.0%)	18 (23.4%)	**p = 0.045**	OR = 2.58, 95% CI = 0.88–7.64, p = 0.086
Periodic discharges	2 (2.7%)	25 (32.5%)	**p < 0.001**	OR = 14.10, 95% CI = 2.73–72.78, **p = 0.002**
IEA	3 (4.1%)	13 (16.9%)	**p = 0.016**	OR = 3.03, 95% CI = 0.66–13.86, p = 0.153

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; EEG, electroencephalographic; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RSWA, rhythmic slow wave activity; SD, standard deviation.

[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.

[b]Variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS), and imaging infarct severity (ASPECTS), using a logistic regression model. First CT ASPECTS was used except in the model including second CT ASPECTS. The ORs for NIHSS, age, and ASPECTS are derived from multivariate logistic models including exclusively these three variables, whereas the ORs for the EEG variables are derived from models including NIHSS, age, ASPECTS, and the respective EEG variable.

Bold values indicate $p \leq 0.05$.

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p = 0.001), and EEG suppression (OR = 7.48, 95% CI = 1.40–39.99, p = 0.019). This model correctly classified 89.0% of the subjects, and the area under the ROC curve was 0.84. The prediction model including this EEG variable did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

In the logistic regression model encompassing known functional outcome predictors of stroke and acute symptomatic seizures (Table 5A), the variables remaining independent predictors were age (OR = 1.06, 95% CI = 1.00–1.12, p = 0.039), NIHSS score (OR = 1.19, 95% CI = 1.07–1.31, p = 0.001) and acute symptomatic seizures (OR = 4.55, 95% CI = 1.34–15.47, p = 0.015). This model correctly classified 91.0% of the subjects, and the area under the ROC curve was 0.82. The prediction model including this type of poststroke seizure did not have a different discriminative capacity compared to the model encompassing the already known outcome predictors.

Discussion

In this work, acute symptomatic seizures were independent predictors of death and remote symptomatic seizures were independent predictors of an unfavorable outcome in the first year after an anterior circulation ischemic stroke. We also demonstrated that EEG abnormalities extracted from visual analysis of a single, early (<72 h after stroke), and short-duration EEG are strong predictors of functional outcome, even when adjusted for previously known (early clinical and imaging) stroke outcome predictors.

We think that the strengths of this work, standing out from previous research in this area, include the sample size of consecutive anterior circulation stroke patients, the prospective nature of a multimodal (clinical, neurophysiological, and imagiological) study, and the 12 months of follow-up with only one patient lost during this period, as well as the adjustment to clinical and infarct severity.

As a limitation, we did not analyze the value of EEG as a functional outcome predictor comparatively with second CT scan or brain MRI, avoiding the inclusion of variables with a high percentage of missing data (17.9% and 58.3%, respectively) in our regression models. Sillanpaa et al.[31] showed the superiority of ASPECTS quantified at 24 h after stroke (over on-admission) noncontrast-enhanced CT in outcome prediction. In our analysis, second CT ASPECTS (but not first CT ASPECTS) was a predictor of stroke functional outcome independently from age and admission NIHSS. Nevertheless, this result must be cautiously interpreted because of the missing data. We acknowledge that our first CT ASPECTS median reflects the difficulty of estimating stroke size from early noncontrast-enhanced CT, reducing the value of this score in functional outcome assessment.

Table 5. Comparison between stroke outcome (mRS ≥ 3 and mRS = 6) prediction model characteristics at 12 months

A. Logistic regression models for an unfavorable outcome (mRS ≥ 3) at 12 months

Model features	Omnibus test[a]	Nagelkerke R^2[b]	Hosmer–Lemeshow test[c]	PAC	SEN	SPE	PPV	NPV	AUC, 95%CI
Independent variables included in the model									
KP[d]	$\chi^2(3) = 52.00$, $p < 0.001$	40.2%	$\chi^2(8) = 3.46$, $p = 0.902$	71.7%	70.3%	73.2%	73.2%	70.3%	0.82, 0.75–0.88
EEG[e]	$\chi^2(1) = 64.00$, $p < 0.001$	46.3%	$\chi^2(0) = 0.00$, —	80.7%	72.7%	89.08	87.5%	75.6%	0.81, 0.74–0.88
KP[d] + EEG[e]	$\chi^2(4) = 93.52$, $p < 0.001$	63.4%	$\chi^2(8) = 4.38$, $p = 0.82$	84.8%	81.1%	88.7%	88.2%	81.8%	0.91, 0.86–0.96
RSS	$\chi^2(1) = 9.88$, $p = 0.002$	8.9%	$\chi^2(0) = 0$, —	60.1%	25.7%	93.2%	78.3%	56.7%	0.59, 0.50–0.69
KP[d] + RSS	$\chi^2(4) = 54.62$, $p < 0.001$	43.3%	$\chi^2(8) = 3.74$, $p = 0.88$	74.8%	72.1%	77.5%	75.4%	74.3%	0.83

B. Logistic regression models for death (mRS = 6) at 12 months

Model features	Omnibus test	Nagelkerke R^2	Hosmer–Lemeshow test	PAC	SEN	SPE	PPV	NPV	AUC, 95%CI
Independent variables included in the model									
KP[d]	$\chi^2(3) = 25.58$, $p < 0.001$	28.2%	$\chi^2(8) = 12.71$, $p = 0.122$	86.9%	22.7%	98.4%	71.4%	87.7%	0.81, 0.70–0.92
EEG[f]	$\chi^2(1) = 10.10$, $p = 0.001$	11.3%	$\chi^2(0) = 0$, —	85.3%	26.1%	96.1%	54.5%	87.8%	0.61, 0.47–0.75
KP[d] + EEG[f]	$\chi^2(4) = 31.21$, $p < 0.001$	33.8%	$\chi^2(8) = 15.39$, $p = 0.052$	89.0%	31.8%	99.2%	87.5%	89.1%	0.84, 0.74–0.93
ASS	$\chi^2(1) = 10.394$, $p = 0.001$	11.6%	$\chi^2(0) = 0$, —	84.7%	0%	100%	0%	84.7%	0.64, 0.51–0.78
ASS + KP[d]	$\chi^2(4) = 31.31$, $p < 0.001$	33.9%	$\chi^2(8) = 20.62$, $p = 0.008$	91.0%	40.9%	100%	100%	90.4%	0.82, 0.70–0.94

ASS, acute symptomatic seizures; AUC, area under receiving operator curve; CI, confidence interval; EEG, electroencephalography; KP, known predictor; mRS, modified Rankin Scale; NPV, negative predictive value; PAC, percentage accuracy in classification (% of cases correctly classified by the model); PPV, positive predictive value; RSS, remote symptomatic seizures; SEN, sensitivity; SPE, specificity.
[a]Omnibus test of model coefficients provides the overall statistical significance of the model, that is, how well the model predicts outcome to no independent variables.
[b]Nagelkerke R^2 is a method of calculating the explained variation, that is, how much variation of the outcome can be explained by the model.
[c]Hosmer–Lemeshow goodness of fit test analyzes how poor the model is at predicting outcome. When not significant, it indicates that the model is not a poor fit.
[d]Known stroke outcome predictors: age, admission National Institutes of Health Stroke Scale and Alberta Stroke Program Early CT Score.
[e]Background activity asymmetry (EEG variable with the highest odds of impacting functional outcome; please refer to Table 4).
[f]EEG suppression (EEG variable with the highest odds of impacting vital outcome; please refer to Table 6).

Table 6. Clinical, imaging, and neurophysiological features and vital outcome at 12 months after anterior circulation ischemic stroke

At 12 months	Death	Alive	Bivariate analysis[a]	Multivariate analysis[b]
Clinical features, n = 150	23	127		
Male	15 (65.2%)	73 (57.5%)	p = 0.488	NA
Mean age (SD)	73.74 (10.08)	66.31 (11.90)	**p = 0.006**	OR = 1.06, 95% CI = 1.01–1.12, **p = 0.028**
Median admission NIHSS (IQR)	18 (7)	11 (10)	**p < 0.001**	OR = 1.18, 95% CI = 0.7–1.3, **p = 0.001**
IV alteplase	18 (78.3%)	83 (65.4%)	p = 0.225	NA
Stroke etiology				
Cardioembolism	10 (43.5%)	67 (52.8%)	NA	NA
Atherosclerosis	5 (21.7%)	31 (24.4%)		
Small vessels	0 (0%)	4 (3.1%)		
Unknown	8 (34.8%)	21 (16.5%)		
Other	0 (0%)	4 (3.1%)		
Acute symptomatic seizures	9 (39.1%)	13 (10.2%)	**p < 0.001**	OR = 4.55, 95% CI = 1.34–15.47, **p = 0.015**
Nonconvulsive status epilepticus	1 (4.3%)	3 (2.4%)	p = 0.587	NA
Remote symptomatic seizures	1 (6.3%)	22 (17.3%)	p = 0.469	NA
Isolated MCA territory infarct, n = 145	22	123		
Median ASPECTS (IQR)	9 (4)	9 (2)	p = 0.295	NA
Second CT, n = 129	22	107		
Hemorrhagic transformation	2 (9.1%)	21 (19.6%)	p = 0.362	NA
First EEG findings, n = 150	23	127		
Background activity slowing	16 (69.6%)	41 (32.3%)	**p = 0.001**	OR = 1.99, 95% CI = 0.66–5.99, p = 0.219
Background activity asymmetry	16 (69.6%)	48 (37.8%)	**p = 0.005**	OR = 1.48, 95% CI = 0.48–4.50, p = 0.495
EEG suppression	6 (26.1%)	5 (3.9%)	**p < 0.001**	OR = 7.48, 95% CI = 1.40–39.99, **p < 0.019**
FSWA	22 (95.7%)	111 (87.4%)	p = 0.251	NA
RSWA	5 (21.7%)	21 (16.5%)	p = 0.544	NA
Periodic discharges	8 (34.8%)	19 (15.0%)	**p = 0.023**	OR = 1.54, 95% CI = 0.48–4.94, p = 0.464
IEA	3 (13.0%)	13 (10.2%)	p = 0.688	NA

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; EEG, electroencephalographic; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RSWA, rhythmic slow wave activity; SD, standard deviation.

[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.

[b]Variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS), and imaging infarct severity (ASPECTS), using a logistic regression model. The ORs for NIHSS, age, and ASPECTS are derived from multivariate logistic models including exclusively these three variables, whereas the ORs for the EEG variables are derived from models including NIHSS, age, ASPECTS, and the respective EEG variable.

Bold values indicate $p \leq 0.05$.

Nevertheless, in the clinical practice of a significant proportion of stroke units (such as ours), a second CT scan is not routinely performed in all patients, unless they had been treated with intravenous alteplase or had a neurological worsening. In our study, using an easy, noninvasive, short-duration, and bedside EEG examination, available in the great majority of neurological departments and intensive care units, we identified neurophysiological independent predictors of stroke outcome in models already including well-established clinical and early imaging outcome prognostic factors.

Poststroke seizures and stroke outcome

In our bivariate analysis, seizures were associated with an unfavorable functional outcome 1 year after stroke, as previously suggested in the literature.[1,3,4,32] It has been postulated in the animal model that poststroke seizures may contribute to tissue damage.[33,34] In addition, De Reuck

et al.[2] showed that remote symptomatic seizures are associated with lesion increase and worsening of disability. As a novel finding, we show that the association between remote seizures and an unfavorable functional outcome 12 months after stroke does remain significant when adjusted for age, and clinical and imaging stroke severity. Furthermore, in our work, acute symptomatic seizures remained as an independent predictor of death in the first year after an anterior circulation stroke, even after adjustment for known stroke outcome predictors. Hesdorffer et al.[1] similarly showed that patients with acute symptomatic seizures (of different etiologies) had a chance 8.9 times higher of dying within 30 days. More recently, Huang et al.[3] also found that patients with seizures during admission for stroke had a higher mortality at 30 days and 1 year. This finding was not observed in a study by Hamidou et al. study,[35] which, however, used a population-based registry and a different definition of early seizures.

EEG abnormalities and stroke outcome

EEG background activity slowing was associated with stroke clinical severity by Kayser-Gatchalian and Neundörfer[7] and, as in our study, with unfavorable stroke outcome by Cillessen et al.[9] The originality of our study resides in the definition of EEG independent predictors of stroke functional outcome, either at short or at long term, even when adjusted for age and clinical and imaging severity of stroke.

The neurophysiological feature with the highest odds of impacting functional outcome was background activity asymmetry. Quantitative EEG studies support our observation. Brain symmetry index obtained from continuous EEG records has been correlated with NIHSS score[36] and lesion volume on MRI.[37] In an easier and simpler way, we showed that background activity asymmetry in raw analysis of a single and short-duration EEG is an independent predictor of unfavorable stroke outcome. Cuspineda and collaborators, using quantitative EEG in 28 patients, showed that this is better than the Canadian Neurological Scale score in residual functional disability prediction[12] and better than the mRS in the prediction of functional outcome.[12,38] In our study, the prognostic models including raw EEG abnormalities correctly classified a higher percentage of patients than the model including exclusively the already known stroke outcome predictors. We believe that our results show that some early EEG characteristics are comparable to clinical stroke severity and better than early CT infarct severity in the determination of poststroke functional outcome, reflecting the concept that EEG is a sensitive neurological diagnosis technique in the detection of acute cerebral ischemia[39] and a robust one in the functional assessment of the brain.[40]

The association between EEG suppression and death deserves attention. Although the low number of patients who died in the hospital does not allow a multivariate analysis, this neurophysiological characteristic has been associated with larger infarcts with a higher risk of becoming malignant,[10] and may draw attention to the need for an early start of medical and/or surgical therapy. In line with our results regarding focal cerebral ischemia outcome, EEG suppression was recently ranked within malignant EEG patterns and as a poor prognostic predictor of postcardiac arrest diffuse cerebral ischemia.[41] In our study, this EEG feature was an independent predictor of the vital outcome 1 year after stroke when controlled for age and stroke severity.

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Conflict of Interest

J.M.F. reports personal fees from Boehringer Ingelheim outside the submitted work. The other authors declare no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Hesdorffer DC, Benn EKT, Cascino GD, et al. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia* 2009;50:1102–1108.
2. De Reuck J, Claeys I, Martens S, et al. Computed tomographic changes of the brain and clinical outcome of patients with seizures and epilepsy after an ischaemic hemispheric stroke. *Eur J Neurol* 2006;13:402–407.
3. Huang CW, Saposnik G, Fang J, et al. Influence of seizures on stroke outcomes: a large multicenter study. *Neurology* 2014;82:768–776.
4. Arntz RM, Rutten-Jacobs LCA, Maaijwee NAM, et al. Poststroke epilepsy is associated with a high mortality after a stroke at young age. *Stroke* 2015;46:2309–2311.
5. Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke: report on a hospital-based stroke cohort. *Neurology* 2000;54:350–354.
6. Knake S, Rochon J, Fleischer S, et al. Status epilepticus after stroke is associated with increased long-term case fatality. *Epilepsia* 2006;47:2020–2026.
7. Kayser-Gatchalian MC, Neundörfer B. The prognostic value of EEG in ischaemic cerebral insults. *Electroencephalogr Clin Neurophysiol* 1980;49:608–617.
8. Ahmed I. Predictive value of the electroencephalogram in acute hemispheric lesions. *Clin Electroencephalogr* 1988;19:205–209.
9. Cillessen JP, van Huffelen AC, Kappelle LJ, et al. Electroencephalography improves the prediction of functional outcome in the acute stage of cerebral ischemia. *Stroke* 1994;25:1968–1972.
10. Schneider AL, Jordan KG. Regional attenuation without delta (RAWOD): a distinctive EEG pattern that can aid in the diagnosis and management of severe acute ischemic stroke. *Am J Electroneurodiagnostic Technol* 2005;45:102–117.
11. Burghaus L, Hilker R, Dohmen C, et al. Early electroencephalography in acute ischemic stroke: prediction of a malignant course? *Clin Neurol Neurosurg* 2007;109:45–49.
12. Cuspineda E, Machado C, Aubert E, et al. Predicting outcome in acute stroke: a comparison between QEEG and the Canadian Neurological Scale. *Clin Electroencephalogr* 2003;34:1–4.
13. Finnigan SP, Rose SE, Walsh M, et al. Correlation of quantitative EEG in acute ischemic stroke with 30-day NIHSS score: comparison with diffusion and perfusion MRI. *Stroke* 2004;35:899–903.
14. Adams HPJ, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of

Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999;53:126–131.
15. Knoflach M, Matosevic B, Rucker M, et al. Functional recovery after ischemic stroke—a matter of age. *Neurology* 2012;78:279.
16. Vogt G, Laage R, Shuaib A, et al. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: an analysis of the Virtual International Stroke Trials Archive (VISTA) database. *Stroke* 2012;43:1266–1272.
17. Barber P, Demchuk A, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000;355:1670–1674.
18. Goldstein L, Bertels C, Davis J. Interrater reliability of the NIH stroke scale. *Arch Neurol* 1989;46:660–662.
19. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin Scale: implications for stroke clinical trials—a literature review and synthesis. *Stroke* 2007;38:1091–1096.
20. Noachtar S, Binnie C, Ebersole J, et al. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999;52:21–41.
21. Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin Neurophysiol* 2013;30:1–27.
22. Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. *Epilepsia* 2013;54:28–29.
23. Adams H, Bendixen B, Kappelle L, et al. Classification of subtype of acute ischemic stroke. *Stroke* 1993;23:35–41.
24. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;55:475–482.
25. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 2010;51:671–675.
26. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* 2008;49:8–12.
27. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56:1515–1523.
28. Leitinger M, Beniczky S, Rohracher A, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus—approach to clinical application. *Epilepsy Behav* 2015;49:158–163.
29. SITS International Stroke Thrombolysis Collaboration. *The SITS Monitoring Study (SITS-MOST). Final study protocol. 2002*. Available at: http://www.acutestroke.org/SM_Protocol/SITS-MOST_final_protocol.pdf. Accessed August 13, 2017.
30. Bentes C, Martins H, Peralta AR, et al. Epileptic manifestations in stroke patients treated with intravenous alteplase. *Eur J Neurol* 2017;24:755–761.
31. Sillanpaa N, Saarinen JT, Rusanen H, et al. CT perfusion ASPECTS in the evaluation of acute ischemic stroke: thrombolytic therapy perspective. *Cerebrovasc Dis Extra* 2011;1:6–16.
32. De Reuck J, De Groote L, Van Maele G. Delayed transient worsening of neurological deficits after ischaemic stroke. *Cerebrovasc Dis* 2006;22:27–32.
33. Fan Y, Deng P, Wang Y-C, et al. Transient cerebral ischemia increases CA1 pyramidal neuron excitability. *Exp Neurol* 2008;212:415–421.
34. Pinard E, Nallet H, MacKenzie ET, et al. Penumbral microcirculatory changes associated with peri-infarct depolarizations in the rat. *Stroke* 2002;33:606–612.
35. Hamidou B, Aboa-Eboulé C, Durier J, et al. Prognostic value of early epileptic seizures on mortality and functional disability in acute stroke: the Dijon Stroke Registry (1985-2010). *J Neurol* 2013;260:1043–1051.
36. van Putten MJAM, Tavy DLJ. Continuous quantitative EEG monitoring in hemispheric stroke patients using the brain symmetry index. *Stroke* 2004;35:2489–2492.
37. Sheorajpanday RVA, Nagels G, Weeren AJTM, et al. Reproducibility and clinical relevance of quantitative EEG parameters in cerebral ischemia: a basic approach. *Clin Neurophysiol* 2009;120:845–855.
38. Cuspineda E, Machado C, Galán L, et al. QEEG prognostic value in acute stroke. *Clin EEG Neurosci* 2007;38:155–160.
39. Jordan K. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. *J Clin Neurophysiol* 2004;21:341–352.
40. Assenza G, Di Lazzaro V. A useful electroencephalography (EEG) marker of brain plasticity: delta waves. *Neural Regen Res* 2015;10:1216–1217.
41. Westhall E, Rossetti AO, van Rootselaar AF, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. *Neurology* 2016;86:1482–1490.

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Quantitative EEG and functional outcome following acute ischemic stroke

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HIGHLIGHTS

- EEG powers in the alpha, beta and delta bands are independent predictors of post-stroke outcome.
- Delta-theta to alpha-beta ratio and alpha relative power are good qEEG stroke outcome predictors.
- Quantitative EEG indices improve the discriminative capacity of outcome models of acute stroke.

ABSTRACT

Objective: To identify the most accurate quantitative electroencephalographic (qEEG) predictor(s) of unfavorable post-ischemic stroke outcome, and its discriminative capacity compared to already known demographic, clinical and imaging prognostic markers.
Methods: Prospective cohort of 151 consecutive anterior circulation ischemic stroke patients followed for 12 months. EEG was recorded within 72 h and at discharge or 7 days post-stroke. QEEG (global band power, symmetry, affected/unaffected hemisphere and time changes) indices were calculated from mean Fast Fourier Transform and analyzed as predictors of unfavorable outcome (mRS $\geq$ 3), at discharge and 12 months poststroke, before and after adjustment for age, admission NIHSS and ASPECTS.
Results: Higher delta, lower alpha and beta relative powers (RP) predicted outcome. Indices with higher discriminative capacity were delta-theta to alpha-beta ratio (DTABR) and alpha RP. Outcome models including either of these and other clinical/imaging stroke outcome predictors were superior to models without qEEG data. In models with qEEG indices, infarct size was not a significant outcome predictor.
Conclusions: DTAABR and alpha RP are the best qEEG indices and superior to ASPECTS in post-stroke outcome prediction. They improve the discriminative capacity of already known clinical and imaging stroke outcome predictors, both at discharge and 12 months after stroke.
Significance: qEEG indices are independent predictors of stroke outcome.

1. Introduction

Stroke is a leading cause of disability and mortality worldwide, and despite advances in disease prevention, acute treatment and rehabilitation, global stroke burden is expected to rise in the future (Feigin et al., 2017). Early post-stroke prognostication is essential both in the short-term (f. ex. in guiding treatment strategies) and

Abbreviations: ADCI, Acute Delta Change Index; ASCI, Acute Symmetry Change Index; ASPECTS, Alberta Stroke Program Early CT score; BSI, Brain Symmetry Index; DTABR, delta-theta to alphabeta ratio; Ln, natural logarithm; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; qEEG, quantitative EEG.

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in the long-term (to aid in rehabilitation management, in order to improve recovery and minimize disability). Predictors of stroke disability and associate death consistently include age and clinical / imaging related stroke severity (Adams et al., 1999; Barber et al., 2000; Frankel et al., 2000; Hankey, 2003; Hankey et al., 2007; Konig et al., 2008; Knoflach et al., 2012; Vogt et al., 2012). However, despite the existence of demographic, clinical and imaging factors that can be associated with functional outcome, early prediction of short and long-term post-stroke outcome is challenging since there is large interindividual variability (Stinear, 2010). Therefore, there is still need to identify reliable, inexpensive biomarkers that can add prognostic information in these patients. Due to accumulating evidence regarding neuro-vascular uncoupling in acute ischemic stroke, neurophysiological biomarkers seem increasingly relevant for predicting outcome (Rossini et al., 2004).

EEG is a non-invasive, inexpensive diagnostic method, with high temporal resolution, contributing to a rapid evaluation of instantaneous brain function. However, its visual interpretation requires technical experience, and may be subject to interrater variability. Hence, quantitative EEG (qEEG) techniques have emerged and have been proven informative in stroke prognostication (Finnigan and van Putten, 2013). These techniques have the advantage of providing objective, rater-independent information, which can be used in a variety of settings, including intensive care units. Previous studies have also shown they can be equal to, or even be more informative, than visual EEG interpretation for detecting cerebral pathology (Sainio et al., 1983; Nuwer et al., 1987; Cillessen et al., 1994; Murri et al., 1998).

In general, EEG parameters such as total power, relative delta and alpha power, ratios between slower and faster frequencies (such as the delta/alpha ratio [DAR] and the [delta + theta/alpha + beta] ratio [DTABR]), and brain symmetry indices (such as the Brain Symmetry Index [BSI] and pair-derived BSI) have been strongly associated with stroke outcome, for up to 12 months (Finnigan and van Putten, 2013). These measures have also been shown, in some studies, to be more reliable in prognostication than standard clinical evaluation (Cuspineda et al., 2003; Finnigan et al., 2007; Diedler et al., 2010; Sheorajpanday et al., 2010, 2011b) or imaging biomarkers (Finnigan et al., 2004; Sheorajpanday et al., 2010, 2011b).

However, direct comparison of these measures and indices for predicting stroke outcome has yielded conflicting results (Finnigan and van Putten, 2013). Moreover, few previous studies attempted to control for independent known outcome factors, such as age at stroke onset, clinical severity at admission or infarct size.

Therefore, the principal objectives of this study were: (1) to identify the most accurate qEEG measure(s) associated with outcome at discharge and 12 months after stroke, (2) to compare the discriminative capacity of outcome models based exclusively in already known demographic, clinical and imaging prognostic markers and including one qEEG variable, and (3) to compare qEEG and visual EEG analysis in stroke outcome prediction, in a large, well defined cohort of acute anterior circulation ischemic stroke patients.

2. Methods

2.1. Study design

Study design has been previously described (Bentes et al., 2017b). We performed a prospective longitudinal study of consecutive anterior circulation ischemic stroke patients admitted to the Stroke Unit of the Neurology Department of a University Hospital, over a period of 24 months (from October 2011 to October 2013) and followed for 12 months. The Ethics Committee "Comissão de Ética para a Saúde" of our hospital approved the study. All subjects or their next of kin gave written informed consent for participation. All included patients had to be previously independent (modified Rankin Scale [mRS] $\leq$ 1), have a National Institutes of Health Stroke Scale score (NIHSS) $\geq$ 4 (Goldstein et al., 1989) upon admission to the emergency department, have an acute ischemic brain lesion (CT scan or MRI) in the internal carotid artery territory and no previous history of epileptic seizures nor traumatic head injury requiring hospital admission.

2.2. Clinical assessment

All patients received standardized clinical and diagnostic assessment, during admission and after discharge. An investigator blinded to the neurophysiological evaluation conducted a phone interview at six months and a clinical appointment 12 months after stroke to access the occurrence of epileptic seizures and functional outcome. Clinical stroke severity was assessed by NIHSS at admission. The functional outcome at discharge and at 12 months was assessed by the mRS scale (Banks and Marotta, 2007).

2.3. Neuroimaging interpretation

A senior neuroradiologist, (C.M. or C.C.) blinded for clinical and electroencephalographic findings analyzed the neuroimaging studies. Doubts were decided by consensus. In patients with middle cerebral artery stroke, infarct size was quantified by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) (Barber et al., 2000) in an acute brain CT (computed tomography) scan performed in the first 24 h after stroke.

2.4. Neurophysiological evaluation

Patients underwent a neurophysiological evaluation protocol that included a 64-channel video-EEG with a maximum duration of 60 min in the first 72 h after stroke (first EEG). A similar EEG was also collected at discharge or on the 7th day post-stroke (second EEG). The neurophysiological protocol was previously described (Bentes et al., 2017a). The record included an eyes-closed, wake resting condition and eyes-open, hyperventilation and photic stimulation activation maneuvers. Raw EEG review was performed by a certified clinical neurophysiologist (CB) using international criteria and terminology (Noachtar et al., 1999; Beniczky et al., 2013; Hirsch et al., 2013), blinded for clinical and imaging findings. All doubts were decided by consensus with another clinical neurophysiologist (ARP).

2.4.1. EEG acquisition

The EEG was recorded in a Nihon-Kohden device with a sample frequency of 1000 Hz. Consecutive samples of EEG, acquired in similar technical conditions (eyes closed, resting condition outside hyperventilation, photic stimulation or sleep) and with the best possible technical quality, were selected forming an EEG segment of 1–10 min.

2.4.2. EEG processing

EEG segments (high cutoff filter 70 Hz; low cutoff filter 0.5 Hz; notch filter 50 Hz, average montage) were exported for FTT analysis in BESA software (BESA Research 6.0, June 2013, BESA GmbH, Graefelting, Germany). In BESA, visual and automatic rejection of artifacts was done. When present, blinking artifacts were also removed by principal component analysis. The EEG was then segmented into 2.05s mini-epochs and FFT analysis was performed for each of these segments. Mean Fast Fourier Transform (FFT) of all the 2.05 s mini-epochs of the selected EEG segment was computed

in the following frequency bands: Delta – 1–4 Hz; Theta – 4–8 Hz; Alfa – 8–12 Hz; Beta – 12–30 Hz. Relative (RP) and absolute power (AP) in these frequency bands was obtained.

2.4.3. Computed indices (qEEG predictors)

Several qEEG indices were calculated from both hemispheres, the affected and unaffected hemisphere, from the first and second EEG recordings, and in the frequency bands described in Section 2.4.2. Details for qEEG index calculation are presented in Supplementary Appendix A.

Computed indices were: global relative power indices including delta, theta, alpha and beta relative power, as well as ratios between slow and fast frequencies (slow (delta-theta) and fast (alfa-beta) frequencies ratio (DTABR), delta and alpha ratio (DAR)). Furthermore, symmetry indices included the brain symmetry index (BSI) and the ratio between affected and unaffected hemisphere RP. We also calculated affected and unaffected hemisphere indices. Lastly, we computed time changes indices, reflecting the dynamic changes between the first (0–72 h) and second EEG (discharge or 7th day post-stroke): Acute Symmetry Change Index (ASCI), Acute Delta, Alpha, Theta and Beta Change Indices, and Acute DTABR Change Index. For simplicity purposes, only results concerning the global relative power indices are reported in the main document. Results from other indices can be found in Supplementary Appendix B. EEG indices were, whenever necessary, transformed to their natural logarithm or square root in order to have normal distribution and homogeneity of variances, as required for logistic regression models.

2.5. Outcomes

The outcomes in this study were an unfavorable functional outcome (mRS $\geq$ 3) at discharge and 12 months after stroke.

2.6. Statistical analysis

EEG spectral indices were evaluated using descriptive statistics (mean and standard deviation) in patients with unfavorable and favorable outcome at discharge (first EEG indices) and 12 months (first, second and dynamic EEG evolution indices) post-stroke. Bivariate analyses were performed between groups using *t*-test after confirming their normal distribution (Shapiro Wilk and Kolmogorov Smirnov tests) or Mann-Whitney test in non-normal variables. Prognostic models were constructed using logistic regression. Homogeneity of variances was confirmed with the Levene test, and model calibration was analyzed by Hosmer-Lemeshow. QEEG variables with a significant association in the bivariate analysis were adjusted for known functional outcome predictors of stroke (Adams et al., 1999; Barber et al., 2000; Knoflach et al., 2012; Vogt et al., 2012), namely age, clinical stroke severity (admission NIHSS) and imaging infarct size (ASPECTS). All logistic models were constructed with only one qEEG variable plus these previously known outcome predictors, in order to avoid the multicolinearity between qEEG variables. Logistic models were performed with the neurophysiological variables in their natural logarithm (Ln) or square root transformation to comply with the model requisites.

Additionally, to assess the overall internal validation of each model, a 10-fold cross-validation technique was implemented. After dividing the dataset into 10 random folds, we used N-1 (9) folds to calculate the model coefficients, which were then applied to the remaining fold to yield fitted values for these observations. The process was repeated 10 times using different folds of the data. Finally, we used the fitted values to obtain a cross-validated area under the ROC curve (cvAUC) and corresponding 95% confidence intervals.

Using DeLong tests, the outcome prediction model including the qEEG index with highest cvAUCs was compared with the model including exclusively known stroke outcome predictors, as well as with models using known predictors and visual EEG analysis variables, namely background activity asymmetry. EEG background asymmetry was chosen in accordance to a previous report where it was shown that this was the variable more strongly associated with anterior circulation ischaemic stroke outcome (Bentes et al., 2017c). Cut-off values were calculated for various sensitivities and specificities. The significance level was $\alpha \leq 0.05$. Statistical analysis was performed using SPSS program version 24 for Mac, and STATA 14.2 for Mac (Statacorp®).

3. Results

3.1. Study population

One-hundred-and-fifty-one patients (112 men and 39 women) were included, with a mean age of 67.4 (S.D. 11.9) years. During the study period, 23 patients died (seven during admission before day 7). One patient (0.66%) was lost for clinical follow-up at 12 months. All patients had at least one acute CT scan and D1 EEG. In 8 patients, D7 EEG was not performed. One patient had bilateral middle cerebral artery stroke and was not included. Study flowchart and further details of the sample studied have been previously described (Bentes et al., 2017c).

3.2. Functional outcome at discharge and at 12 months

3.2.1. Bivariate analyses

All patients were included in the analysis. The average duration of the EEG segments used for FFT calculation, after artifact removal was 248 ± 222 s (median 213 s). Tables 1 and 2 show the main qEEG indices calculated for patients who were alive and independent at discharge and at 12 months, respectively, as compared to patients who died or were dependent at these time points. Most qEEG indices show significant differences between these two groups. Overall, dependence or death at discharge is associated with EEGs with higher slow frequency (delta) and lower high frequency (alpha and beta) powers, both in overall EEG power and in each hemisphere separately (affected and unaffected). Further results from the bivariate analysis are found in Supplementary Appendix B.

3.2.2. Multivariate analyses

On multivariate analysis, after controlling for admission NIHSS, age and ASPECTS, most of the neurophysiological variables remained independent predictors of outcome (Supplementary Appendix B).

After 10-fold cross-validation, the variables rendering models with highest cvAUC were DTABR, and alpha RP. Therefore, models including DTABR or alpha RP were chosen for ROC comparison with both the known functional outcome predictors model and the model with visual EEG analysis of background asymmetry (Fig. 1). While DTABR is associated with the highest cvAUC both at discharge and 12 months, alpha RP was chosen because it is easy to calculate and is less prone to be interfered by artifacts than qEEG indices including lower frequencies.

Table 3 displays the comparison between stroke outcome prediction models characteristics at discharge and 12 months post-stroke. For discharge outcome, compared with the known functional outcome predictors model (cvAUC 0.752, 95% CI 0.671–0.834), both models including DTABR (cvAUC 0.827, 95% CI 0.758–0.895) or alpha RP (cvAUC 0.814, 95% CI 0.742–0.885) preform significantly better (DeLong tests: $p = 0.009$ and $p = 0.023$, respectively). The discriminative capacity of models including DTABR or alpha RP was similar (DeLong tests $p = 0.3525$).

Table 1
Quantitative EEG indices and outcome at discharge.

qEEG index	mRS < 3 (n = 52)	mRS ≥ 3 (n = 99)	Bivariate analysis p	Multivariate analysis OR (95%CI) p	Cross-validated AUC (95% CI)
1st EEG (0–72 h)					
Delta RP	0.37 ± 0.17 (0.37)	0.54 ± 0.17 (0.54)	<0.001*	125.0 (9.2–1692.4) <0.001[a]	0.812 (0.740–0.884)
Theta RP	0.20 ± 0.08 (0.21)	0.22 ± 0.09 (0.20)	n.s.*	–	–
Alpha RP	0.23 ± 0.12 (0.22)	0.13 ± 0.08 (0.11)	<0.001*	0.221 (0.099–0.492) <0.001[b]	0.814 (0.742–0.885)
Beta RP	0.20 ± 0.13 (0.18)	0.12 ± 0.08 (0.09)	<0.001*	0.28 (0.140–0.574) <0.001[b]	0.803 (0.729–0.877)
DTABR	1.87 ± 1.45 (1.51)	4.61 ± 3.29 (4.01)	<0.001*	1.702 (1.297–2.231); p < 0.001[a]	0.827 (0.758–0.895)

Results in the 2nd and 3rd column are shown as mean ± standard deviation (median) of the natural logarithm of the EEG index. Multivariate analyses included the variables age, NIHSS at admission and ASPECTS scores plus the EEG index. CI 95% – 95% confidence interval; OR – odds ratio; RP – relative power; DTABR – delta-theta to alpha-beta ratio.
* *t*-test.
* Mann-Whitney *U* test.
[a] Logistic regression using the untransformed variable.
[b] Logistic regression using the variable transformed into the natural logarithm.

Table 2
Quantitative EEG indices and outcome at 12 months.

qEEG index	mRS < 3 (n = 73)	mRS ≥ 3 (n = 77)	Bivariate analysis p	Multivariate OR (95%CI) p	Cross-validated AUC (95% CI)
1st EEG (0–72 h)					
Delta RP	0.41 ± 0.17 (0.40)	0.56 ± 0.17 (0.58)	<0.001*	129.8 (8.8–1904.5) <0.001[a]	0.836 (0.771–0.900)
Theta RP	0.20 ± 0.09 (0.20)	0.22 ± 0.09 (0.22)	n.s.*	–	–
Alpha RP	0.21 ± 0.11 (0.17)	0.12 ± 0.08 (0.11)	<0.001*	0.16 (0.064–0.380) <0.001[b]	0.852 (0.790–0.913)
Beta RP	0.19 ± 0.12 (0.16)	0.11 ± 0.08 (0.08)	<0.001*	0.28 (0.137–0.572) <0.001[b]	0.829 (0.763–0.895)
DTABR	2.17 ± 1.56 (1.68)	5.12 ± 3.46 (4.15)	<0.001*	1.668 (1.297–2.143) p < 0.001[a]	0.859 (0.800–0.919)
2nd EEG (day 7 or discharge)					
Delta RP	0.37 ± 0.16 (0.33)	0.57 ± 0.19 (0.57)	<0.001*	165.4 (13.43–2036.1) <0.001[a]	0.833 (0.768–0.899)
Theta RP	0.19 ± 0.10 (0.15)	0.20 ± 0.09 (0.18)	n.s.*	–	–
Alpha RP	0.24 ± 0.13 (0.22)	0.13 ± 0.10 (0.10)	<0.001*	0.001 (0.000–0.027) <0.001[c]	0.827 (0.760–0.894)
Beta RP	0.21 ± 0.13 (0.18)	0.10 ± 0.09 (0.08)	<0.001*	0.319 (0.17–0.60) <0.001[b]	0.819 (0.750–0.888)
DTABR	1.88 ± 1.89 (1.25)	10.64 ± 35.91 (4.15)	<0.001*	3.17 (1.86–5.42) p < 0.001[a]	0.843 (0.779–0.907)

Results in the 2nd and 3rd column are shown as mean ± standard deviation (median) of the natural logarithm of the EEG index. Multivariate analyses included the variables age, NIHSS at admission and ASPECTS scores plus the EEG index. OR – odds ratio; RP – relative power; DTABR – delta-theta to alpha-beta ratio.
* *t*-test.
* Mann-Whitney *U* test.
[a] Logistic regression using the untransformed variable.
[b] Logistic regression using the variable transformed into the natural logarithm.
[c] Logistic regression using the variable transformed into the square root.

Analogously, for 12-month outcome, compared with the model with known functional outcome predictors (cvAUC 0.794, 95% CI 0.722–0.865), both models including DTABR (cvAUC 0.859, 95% CI 0.800–0.919) and alpha RP (cvAUC 0.852, 95% CI 0.790–0.913) had significantly higher discriminative capacity (DeLong tests: p = 0.009 and p = 0.015, respectively). As for discharge, the predictive power of models including DTABR or alpha RP was similar (DeLong tests p = 0.5482).

Moreover, for both discharge and 12-month unfavorable outcome, NIHSS remains as the only independent predictor together with any of the two qEEG indices.

Finally, visual analysis of EEG background asymmetry was also an independent prognostic marker of poor functional outcome at discharge (cvAUC 0.831, 95% CI 0.762–0.900) and 12 months (cvAUC 0.890, 95% CI 0.837–0.943) and performed significantly better than the known functional outcome predictors model alone (DeLong test: 0.010 for discharge and 0.001 for 12 months). The discriminative capacity of the model incorporating visual EEG analysis was not significantly different compared with models with either qEEG index (DTABR – DeLong test: 0.767 for discharge and 0.185 for 12 months; alpha RP – DeLong test: 0.190 for discharge and 0.100 for 12 months).

3.2.2.1. Cutoff values for alpha relative power in the first EEG. Table 4 shows the sensitivity and specificity values for alpha RP obtained from the first EEG, for predicting unfavorable outcome.

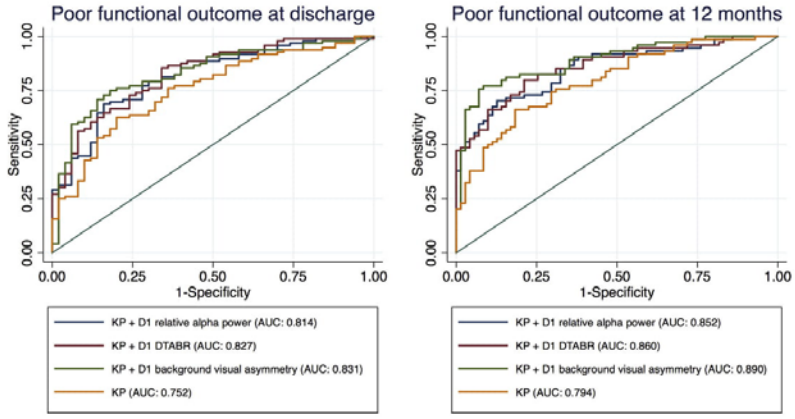

Fig. 1. Receiver Operating Characteristic (ROC) curves for multivariate models including known post-stroke outcome predictors (KP – age, admission NIHSS and ASPECTS), with or without one additional qEEG index (DTABR – delta-theta to alfa-beta ratio or alpha RP – relative power) obtained from the quantitative analysis of the first EEG or visual EEG analysis (background asymmetry) of the same record, in relation to poor functional outcome at discharge (A) and 12 months (B).

Table 3
Comparison between stroke outcome (mRS ≥ 3) prediction models characteristics at discharge (A) and 12 months (B).

Model	Omnibus Test	Nagelkerkes R^2	Hosmer & Lemeshow test	PAC (%)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	Cross-validated AUC (95% CI)
A. Unfavorable outcome at discharge									
KP[a]	$\chi^2(3) = 34.94$; p < 0.001	0.294	$\chi^2(8) = 4.90$; p = 0.768	73.3	85.4	50.0	76.6	64.1	0.752 (0.671–0.834)
Alpha RP[b]	$\chi^2(1) = 28.5$; P < 0.001	0.238	$\chi^2(8) = 10.1$; p = 0.259	72.8	86.9	46.2	75.4	64.9	0.756 (0.674–0.838)
DTABR[b]	$\chi^2(1) = 37.3$; P < 0.001	0.302	$\chi^2(8) = 4.74$; p = 0.785	71.5	84.8	46.2	75.0	61.5	0.785 (0.710–0.860)
KP[a] + alpha RP[b]	$\chi^2(4) = 50.79$; p < 0.001	0.406	$\chi^2(8) = 5.07$; p = 0.751	76.7	85.4	60.0	80.4	68.2	0.814 (0.742–0.885)
KP[a] + DTABR[b]	$\chi^2(4) = 3.73$; p < 0.001	0.426	$\chi^2(8) = 4.44$; p = 0.816	78.1	87.5	60.0	80.7	71.4	0.827 (0.758–0.895)
KP[a] + visually analyzed EEG background asymmetry	$\chi^2(4) = 59.25$; p < 0.001	0.461	$\chi^2(8) = 3.67$; p = 0.885	76.7	81.3	68.0	82.9	65.4	0.831 (0.762–0.900)
KP[a] + visually analyzed EEG background slowing[b]	$\chi^2(4) = 46.61$; p < 0.001	0.378	$\chi^2(8) = 5.01$; p = 0.756	74.7	82.3	60	79.8	63.8	0.787 (0.713–0.861)
B. Unfavorable outcome at 12 months									
KP[a]	$\chi^2(3) = 52.15$; p < 0.001	0.403	$\chi^2(8)=5.20$; p = 0.736	71.0	70.3	71.8	72.2	69.8	0.794 (0.722–0.865)
Alpha RP[b]	$\chi^2(1) = 36.42$; p < 0.001	0.287	$\chi^2(8) = 15.6$; p = 0.048	68.0	70.1	65.8	68.4	67.6	0.768 (0.692–0.844)
DTABR[b]	$\chi^2(1) = 40.52$; p < 0.001	0.316	$\chi^2(8) = 9.98$; p = 0.266	70.7	76.6	64.4	69.4	72.3	0.774 (0.697–0.850)
KP[a] + alpha RP[b]	$\chi^2(4) = 73.48$p < 0.001	0.530	$\chi^2(8) = 6.61$; p = 0.579	77.2	75.7	78.9	78.9	75.6	0.852 (0.790–0.913)
KP[a] + DTABR[b]	$\chi^2(4) = 73.15$; p < 0.001	0.528	$\chi^2(8) = 8.78$; p = 0.361	77,2	79,7	74,6	76.6	77.9	0.859 (0.800–0.919)
KP[a] + visually analyzed EEG background asymmetry	$\chi^2(4) = 93.52$; p < 0.001	0.634	$\chi^2(8) = 4.38$; p = 0.82	84.8	81.1	88.7	88,2	81,8	0.890 (0.837–0.943)
KP[a] + visually analyzed EEG background slowing[b]	$\chi^2(4) = 83.169$; p < 0.001	0.582	$\chi^2(8) = 5.96$; p = 0.652	82.8	78.4	87.3	84.1	79.5	0.866 (0.808–0.924)

KP – known post-stroke outcome predictors (age, admission NIHSS, 1st CT ASPECTS score); RP – relative power; DTABR – delta-theta to alpha-beta ratio; PAC – Percentage accurately classified; SEN – sensitivity; SPE – specificity; PPV – positive predictive value; NPV – negative predictive value; AUC – area under the ROC curve; CI – confidence interval.

[a] Age and ASPECTS are non-significant variables in the model.

[b] 1st EEG (0–72 h).

This neurophysiological variable, in isolation, predicts unfavorable outcome with an area under the ROC curve of 0.750 (95% CI 0.669–0.832) at discharge and 0.769 (95%CI 0.695–0.844) at 12 months. For both discharge and 12-month outcomes, an alpha RP lower than 10% on an EEG performed in the first 72 h post-stroke shows high specificity to predict unfavorable outcome (87–89%), despite low sensitivity (37–46%). Alpha RP below 20% have higher sensitivity to detect patients with unfavorable outcome (86 and 90%, respectively) albeit low specificity.

Table 4
Sensitivity and specificity of different Ln D1 alpha RP values for predicting unfavorable outcome.

1st EEG (0–72 h)	Sensitivity	Specificity
Death or functional dependency at discharge (mRS ≥ 3)		
Ln alpha RP ≤ −2.3 (alpha RP ≤ 10%)	37–46%	87–89%
Ln alpha RP ≤ −1.9 (alpha RP ≤ 15%)	66–70%	67–71%
Ln alpha RP ≤ −1.6 (alpha RP ≤ 20%)	86%	52–54%
Death or functional dependency at 12-month post-stroke (mRS ≥ 3)		
Ln alpha RP ≤ −2.3 (alpha RP ≤ 10%)	46–53%	86–89%
Ln alpha RP ≤ −1.9 (alpha RP ≤ 15%)	71–77%	53–66%
Ln alpha RP ≤ −1.6 (alpha RP ≤ 20%)	90%	44–45%

Ln – natural logarithm; RP – relative power.

4. Discussion

To the best of our knowledge, this is the largest study evaluating quantitative EEG parameters for prediction of post-stroke functional outcome. In a consecutively selected, well defined, acute anterior circulation ischemic stroke cohort, the predictive accuracy of qEEG measures was examined while controlling for clinical and imaging variables, which are available and easily determined in clinical practice in a stroke unit.

In this study, comparing absolute and relative frequency band power indices, symmetry measures and dynamic time changes, we have shown that most qEEG indices previously reported in the literature are independent prognostic markers for poor functional outcome. Additionally, DTABR and alpha RP are some of the most accurate neurophysiological markers for outcome prediction, both at discharge and 12 months after stroke. Lower alpha RP, higher DTABR and higher NIHSS scores were sufficient to predict poor functional outcome, rendering age and ASPECTs scores non-significant in our models. Furthermore, these qEEG indices seem to provide additional prognostic information to already known clinical and imaging-related predictors, and with similar performance to previously reported visual EEG analysis of background asymmetry. Finally, we report that alpha RP below 10% is highly specific for a poor functional outcome at both timelines.

Negative correlation between alpha activity and stroke outcome is in accordance with several previous studies (Sainio et al., 1983; Szelies et al., 2002; Cuspineda et al., 2007; Finnigan et al., 2007; Diedler et al., 2010; Schleiger et al., 2014). Alpha frequencies are thought to derive from cortical layers IV and V, whereas slower delta or theta frequencies are generated by the thalamus and cortical layers II-VI (Schuijt et al., 2012). Therefore, it is not surprising that alpha activity disturbances reflect direct cortical injury (Kaplan and Rossetti, 2011). Furthermore, the change in faster frequencies, such as alpha, is thought to precede the increase in slower frequencies, as shown in patients undergoing carotid endarterectomy with continuous EEG and cerebral blood flow measurements (Sharbrough et al., 1973). In 47 patients with unilateral cerebral infarction, relative alpha frequency positively correlated with regional cerebral blood flow and oxygen metabolism, as measured by positron emission tomography (Nagata et al., 1989). The same variable has been positively correlated with cognitive outcome (in a functional assessment scale), as well as with improvement in post-stroke aphasia (Szelies et al., 2002; Schleiger et al., 2014). This assessment might be even extended to critical care ventilated patients, where a decrease in faster frequency activity has been associated with drop in cerebral perfusion pressure (Diedler et al., 2009). In patients presenting with subarachnoid hemorrhage, relative alpha power was able to predict the development of delayed cerebral ischemia (Rathakrishnan et al., 2011). Moreover, alpha activity may rapidly increase after successful reperfusion due to rt-PA administration in acute stroke (Finnigan et al., 2006). In a previous study, we have shown that, in visual EEG analysis, the variables more strongly associated with outcome were background activity slowing and background activity asymmetry (Bentes et al., 2017c). On visual analysis, background slowing is usually related to a decrease in alpha frequency or absent alpha activity. Therefore, the qEEG findings are in accordance with the visual analysis.

Other neurophysiological variables (DTABR, DAR, delta RP), also strongly and independently associated with outcome, incorporate lower frequencies, such as delta power. Delta oscillations usually emerge and have higher voltage in the core lesion of ischemic stroke patients (Murri et al., 1998). They may be more predominant on the affected hemisphere, but their presence in the unaffected side, as measured by EEG and magnetoencephalography, has been described as an important prognostic factor (Finnigan et al., 2007; Tecchio et al., 2007; Assenza et al., 2013). In our sample, the DTABR was the qEEG index that was associated with higher discriminative power in AUC analysis to detect short and long-term poor prognosis after stroke. DTABR correlates negatively with cerebral perfusion accessed by Position Emission Tomography in stroke patients (Nagata et al., 1989) and as been shown to be very sensitive and specific for discriminating between cerebral ischemia and controls (Finnigan et al., 2015) and to be an independent prognostic factor for short-term disability after lacunar stroke (Sheorajpanday et al., 2011a). Sub-acute DTABR also predicted 6 months-disability in an unselected population of stroke patients (Sheorajpanday et al., 2011b). Our data reinforces the importance of this qEEG parameter as a strong predictor for short and long term functional stroke outcome, when obtained as early as the first 72 h after stroke.

To the best of our knowledge, no previous study directly compared the accuracy of alpha RP and DTABR as functional stroke outcome predictors. Our data suggests that they are not significantly different. In our study, we focused on reporting the predictive value of alpha RP for several reasons. Firstly, our data has shown that models with DTABR and alpha RP have similar discriminative capacities. DTABR, besides requiring a more specific computation, incorporates the delta frequency band that is more frequently interfered by artifacts such as blinking, slow shifts or sudation. In the clinical setting, where continuous EEG signal might not be submitted to the strict scrutiny for artifacts, as in this research, its value may not be comparable. Overall, alpha RP seems a preferable neurophysiological marker as it analyses the brain oscillatory activity with higher signal to noise ratio on scalp EEG. Furthermore, some EEG patterns, such as Rapid Attenuation Without Delta, may not be detected analyzing delta frequencies, and may be present in large occlusive infarcts with poor outcome (Schneider and Jordan, 2005).

In other studies, qEEG brain symmetry parameters have been associated with functional outcome (van Putten and Tavy, 2004; de Vos et al., 2008; Sheorajpanday et al., 2009, 2010, 2011b). In our study, however, qEEG symmetry indices were not significant on multivariate analysis. We used an average montage before performing spectral analysis, which may reduce asymmetries between oscillatory brain activities.

We have also shown that the discriminative capacity of EEG characteristics obtained from visual EEG analysis is similar to qEEG indices. This is an important finding, as visual EEG analysis is cumbersome and dependent on trained neurophysiologists. In contrast, qEEG indices can be readily and easily available in a stroke unit and can be interpreted by all health personnel.

One important finding in our study is the weaker effect of CT imaging lesion size (ASPECTS), obtained from the first CT scan after stroke, when compared to DTABR and alpha RP in outcome prediction. To date, no previous study has compared ASPECTS with qEEG parameters in outcome prediction. Although neuroimaging with CT adds invaluable diagnostic information for stroke patients, this technique has several limitations regarding lesion volume determination especially in the acute/hyperacute phase (Sillanpaa et al., 2011). During this period, qEEG data may be more reliable and easy to monitor, especially in intensive care settings.

Several limitations of this work are common to other qEEG studies. Effective identification and exclusion of EEG artifacts may be a challenge, such as muscle artifacts interfering with faster activities, or eye movements with delta activity. In our study, besides using an automatic method for artifact removal, an additional visual rejection was done. This may render the results less applicable to qEEG measures in intensive care units, when depending solely upon automatic artifact removal. These results were also obtained from 62-channels EEG that are not routine for EEG monitoring. Further studies are necessary to validate these data.

In conclusion, in a large, well defined cohort of acute anterior ischemic stroke patients, we found that the alpha RP or DTABR are qEEG variables that contribute significantly for post-stroke outcome prediction, at discharge and 12 months after stroke, when controlled for demographic, clinical and imaging variables.

5. Conflict of interest statement

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2018.05.021.

References

Adams HPJ, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH stroke scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126–31.

Assenza G, Zappasodi F, Pasqualetti P, Vernieri F, Tecchio F. A contralesional EEG power increase mediated by interhemispheric disconnection provides negative prognosis in acute stroke. Restor Neurol Neurosci 2013;31:177–88.

Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: implications for stroke clinical trials – a literature review and synthesis. Stroke 2007;38:1091–6.

Barber P, Demchuk A, Zhang J, Buchan A. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;355:1670–4.

Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013;54 (Suppl. 6):28–9.

Bentes C, Martins H, Peralta AR, Casimiro C, Morgado C, Franco AC, et al. Post-stroke seizures are clinically underestimated Available from:. J Neurol 2017a;264:1978–85. http://link.springer.com/10.1007/s00415-017-8586-9.

Bentes C, Martins H, Peralta AR, Morgado C, Casimiro C, Franco AC, et al. Epileptic manifestations in stroke patients treated with intravenous alteplase Available from:. Eur J Neurol 2017b;24:755–61. http://doi.wiley.com/10.1111/ene.13292.

Bentes C, Peralta AR, Martins H, Casimiro C, Morgado C, Franco AC, et al. Seizures, electroencephalographic abnormalities, and outcome of ischemic stroke patients Available from:. Epilepsia Open 2017c;2:441–52. http://doi.wiley.com/10.1002/epi4.12075.

Cillessen JP, van Huffelen AC, Kappelle LJ, Algra A, van Gijn J. Electroencephalography improves the prediction of functional outcome in the acute stage of cerebral ischemia Available from:. Stroke 1994;25:1968–72. http://www.ncbi.nlm.nih.gov/pubmed/8091439.

Cuspineda E, Machado C, Aubert E, Galan L, Llopis F, Avila Y. Predicting outcome in acute stroke: a comparison between QEEG and the Canadian Neurological Scale Available from:. Clin Electroencephalogr 2003;34:1–4. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12515444.

Cuspineda E, Machado C, Galán L, Aubert E, Alvarez MA, Llopis F, et al. QEEG prognostic value in acute stroke. Clin EEG Neurosci 2007;38:155–60.

de Vos CC, Van Maarseveen SM, Brouwers PJ, van Putten MJ. Continuous EEG monitoring during thrombolysis in acute hemispheric stroke patients using the brain symmetry index. J Clin Neurophysiol 2008;25:77–82.

Diedler J, Sykora M, Bast T, Poli S, Veltkamp R, Mellado P, et al. Quantitative EEG correlates of low cerebral perfusion in severe Stroke. Neurocrit Care 2009;11:210–6.

Diedler J, Sykora M, Jüttler E, Veltkamp R, Steiner T, Rupp A. EEG power spectrum to predict prognosis after hemicraniectomy for space-occupying middle cerebral artery infarction. Cerebrovasc Dis 2010;29:162–9.

Feigin VL, Norrving B, Mensah GA. Global burden of stroke. Circ Res 2017;120.

Finnigan S, van Putten MJAM. EEG in ischaemic stroke: quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. Clin Neurophysiol 2013;124:10–9. Available from: http://dx.doi.org/10.1016/j.clinph.2012.07.003.

Finnigan S, Wong A, Read S. Defining abnormal slow EEG activity in acute ischaemic stroke: delta/alpha ratio as an optimal QEEG index Available from:. Clin Neurophysiol 2015;127:1452–9. http://linkinghub.elsevier.com/retrieve/pii/S1388245715007233.

Finnigan SP, Rose SE, Chalk JB. Rapid EEG changes indicate reperfusion after tissue plasminogen activator injection in acute ischaemic stroke. Clin Neurophysiol 2006;117:2338–9.

Finnigan SP, Rose SE, Walsh M, Griffin M, Janke AL, McMahon KL, et al. Correlation of quantitative EEG in acute ischemic stroke with 30-day NIHSS score: comparison with diffusion and perfusion MRI Available from:. Stroke 2004;35:899–903. http://www.ncbi.nlm.nih.gov/pubmed/15001786.

Finnigan SP, Walsh M, Rose SE, Chalk JB. Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. Clin Neurophysiol 2007;118:2525–32.

Frankel M, Morgenstern L, Kwiatkowski T, Lu M, Tilley B, Broderick J, et al. Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA stroke trial. Neurology 2000;55:952–9.

Goldstein L, Bertels C, Davis J. Interrater reliability of the NIH stroke scale. Arch Neurol 1989;46:660–2.

Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack Available from:. Cerebrovasc Dis 2003;16(Suppl 1):14–9. https://www.karger.com/Article/FullText/69936.

Hankey GJ, Spiesser J, Hakimi Z, Bego G, Carita P, Gabriel S. Rate, degree, and predictors of recovery from disability following ischemic stroke. Neurology 2007;68:1583–7.

Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American clinical neurophysiology society's standardized critical care EEG terminology: 2012 version. J Clin Neurophysiol 2013;30:1–27.

Kaplan PW, Rossetti AO. EEG patterns and imaging correlations in encephalopathy: encephalopathy part II. J Clin Neurophysiol 2011;28:233–51.

Knoflach M, Matosevic B, Rucker M, Furtner M, Mair A, Wille C, et al. Functional recovery after ischemic stroke – a matter of age. Neurology 2012;78:279.

Konig IR, Ziegler A, Bluhmki E, Hacke W, Bath PMW, Sacco RL, et al. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. Stroke 2008;39:1821–6.

Murri L, Gori S, Massetani R, Bonanni E, Marcella F, Milani S. Evaluation of acute ischemic stroke using quantitative EEG: a comparison with conventional EEG and CT scan Available from:. Neurophysiol Clin 1998;28:249–57. http://www.ncbi.nlm.nih.gov/pubmed/9686400%5Cnhttp://ac.els-cdn.com/S0987705398801159/1-s2.0-S0987705398801159-main.pdf.

Nagata K, Tagawa K, Hiroi S, Shishido F, Uemura K. Electroencephalographic correlates of blood flow and oxygen metabolism provided by positron emission tomography in patients with cerebral infarction Available from:. Electroencephalogr Clin Neurophysiol 1989;72:16–30. http://www.ncbi.nlm.nih.gov/pubmed/2464472.

Noachtar S, Binnie C, Ebersole J, Mauguière F, Sakamoto A, Westmoreland B. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings Available from:. Int Feder Clin Neurophysiol Electroencephalogr Clin Neurophysiol Suppl 1999;52:21–41. http://www.ncbi.nlm.nih.gov/pubmed/10590974.

Nuwer MR, Jordan SE, Ahn SS. Evaluation of stroke using EEG frequency analysis and topographic mapping Available from:. Neurology 1987;37:1153–9. http://www.ncbi.nlm.nih.gov/pubmed/3601079.

Rathakrishnan R, Gotman J, Dubeau F, Angle M. Using continuous electroencephalography in the management of delayed cerebral ischemia following subarachnoid hemorrhage. Neurocrit Care 2011;14:152–61.

Rossini PM, Altamura C, Ferretti A, Vernieri F, Zappasodi F, Caulo M, et al. Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? Brain 2004;127:99–110.

Sainio K, Stenberg D, Keskimaki I, Muuronen A, Kaste M. Visual and spectral EEG analysis in the evaluation of the outcome in patients with ischemic brain infarction. Electroencephalogr Clin Neurophysiol 1983;56:117–24.

Schleiger E, Sheikh N, Rowland T, Wong A, Read S, Finnigan S. Frontal EEG delta/alpha ratio and screening for post-stroke cognitive deficits: the power of four electrodes. Int J Psychophysiol 2014;94:19–24. Available from: http://dx.doi.org/10.1016/j.ijpsycho.2014.06.012.

Schneider AL, Jordan KG. Regional attenuation without delta (RAWOD): a distinctive EEG pattern that can aid in the diagnosis and management of severe acute ischemic stroke Available from:. Am J Electroneurodiagnostic Technol 2005;45:102–17. http://www.ncbi.nlm.nih.gov/pubmed/15989073.

Schuijt TJ, Van Der Poll T, Wiersinga WJ. In: Annual update in intensive care and emergency medicine; 2012. p. 29–37. Available from: http://link.springer.com/10.1007/978-3-642-25716-2.

Sharbrough FW, Messick Jr JM, Sundt Jr TM. Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy Available from:. Stroke 1973;4:674–83. http://stroke.ahajournals.org/cgi/doi/10.1161/01.STR.4.4.674.

Sheorajpanday RVA, Nagels G, Weeren AJTM, De Deyn P. Quantitative EEG in ischemic stroke: correlation with infarct volume and functional status in posterior circulation and lacunar syndromes. Clin Neurophysiol 2011a;122:884–90. Available from: http://dx.doi.org/10.1016/j.clinph.2010.08.020.

Sheorajpanday RVA, Nagels G, Weeren AJTM, van Putten MJAM, De Deyn PP. Reproducibility and clinical relevance of quantitative EEG parameters in cerebral ischemia: a basic approach. Clin Neurophysiol 2009;120:845–55.

Sheorajpanday RVA, Nagels G, Weeren AJTM, van Putten MJAM, De Deyn PP. Quantitative EEG in ischemic stroke: correlation with functional status after 6months. Clin Neurophysiol 2011b;122:874–83.

Sheorajpanday RVA, Nagels G, Weeren AJTM, De Surgeloose D, De Deyn PP. Additional value of quantitative EEG in acute anterior circulation syndrome of presumed ischemic origin. Clin Neurophysiol 2010;121:1719–25.

Sillanpaa N, Saarinen JT, Rusanen H, Hakomaki J, Lahteela A, Numminen H, et al. CT perfusion ASPECTS in the evaluation of acute ischemic stroke: thrombolytic therapy perspective Available from:. Cerebrovasc Dis Extra 2011;1:6–16. http://www.karger.com/doi/10.1159/000324324.

Stinear C. Prediction of recovery of motor function after stroke. Lancet Neurol 2010;9:1228–32.

Szelies B, Mielke R, Kessler J, Heiss WD. Prognostic relevance of quantitative topographical EEG in patients with poststroke aphasia. Brain Lang 2002;82:87–94.

Tecchio F, Pasqualetti P, Zappasodi F, Tombini M, Lupoi D, Vernieri F, et al. Outcome prediction in acute monohemispheric stroke via magnetoencephalography. J Neurol 2007;254:296–305.

van Putten MJAM, Tavy DLJ. Continuous quantitative EEG monitoring in hemispheric stroke patients using the brain symmetry index Available from:. Stroke 2004;35:2489–92. http://stroke.ahajournals.org/cgi/doi/10.1161/01.STR.0000144649.49861.1d.

Vogt G, Laage R, Shuaib A, Schneider A. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: An analysis of the Virtual International Stroke Trials Archive (VISTA) database. Stroke 2012;43:1266–72.

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